FEVER

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F E V E R

A CLINICAL STUDY

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CONTENTS.

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THE THEORY OF FEVER.

Fever is not a distinct entity, but a collection of various phenomena the co-existence of which in the system is conveniently characterised by the term 'fever.' Of these phenomena the most constant and characteristic is increased body heat. So prominent is this feature of the febrile state that a rise of temperature is generally referred to as fever: a patient whose temperature is raised is said to be feverish, and the terms 'fever' and 'increased body heat' have come to be regarded as synonymous. Thus in our own day, as in the days of Galen, *calor præter naturam* is looked upon as the pathognomonic feature of fever.

A more intimate acquaintance with the phenomena which go to constitute the febrile state, and the generally more accurate knowledge of the bedside phenomena of disease which has resulted from the use of the clinical thermometer, have shown us that 'fever' and 'rise of temperature' cannot with strict accuracy be regarded as synonymous terms. There may be fever without rise of temperature (as in the advanced stages of some bad cases of pneumonia and of typhus), and there may be rise of temperature without true fever, as in some cases of cerebral disease. But though there is thus good reason why increased

body heat should not be regarded as the pathognomonic and essential feature of fever, it is not possible to substitute for it a better or more convenient clinical test of the existence of fever, or one which is so serviceable at the bedside. For practical purposes, therefore, rise of temperature may still be regarded as the test of the existence of fever and its extent as the index to the amount of febrile disturbance.

The physiological facts which have to be kept before us in considering the theory of fever are as follows:—1. Two main processes are constantly going on in the system—tissue formation and tissue disintegration. 2. During tissue disintegration there are formed various products destined for elimination; the chief of these are urea, carbonic acid, and heat. 3. Urea is eliminated by the kidneys, carbonic acid by the lungs, and heat by the skin. 4. In the case of each, production and elimination are so well balanced that no accumulation takes place in the system. 5. In the case of heat this balance is so well maintained that the normal temperature is always the same (98·4° F.). 6. The various processes here indicated are presided over by the nervous centres, and it is by the regulating power of these centres that the normal balance is maintained.

In fever the whole process is disturbed; there is increased formation of urea and carbonic acid, and the temperature rises above 98·4°. All theories of fever essentially consist in an attempt to account for the rise of temperature. The readiest and most natural way of doing so is to attribute it to increased activity of the processes which keep up the normal temperature. We accordingly find that the most generally accepted of the modern theories of fever—the so-called combustion theory—is that which attributes it to such increase. 'Fever,' says Virchow, 'essentially consists in elevation of temperature, which must arise from an increased consumption of tissue, and appears to have its immediate cause in alterations of the nervous system.' Liebermeister defines it 'as a symptom-group, at the foundation of which is an elevation of the temperature of the body produced by a morbid general increase of metamorphosis.'

The evidence of increased tissue metamorphosis in fever

is the wasting of the tissues, and the increased elimination of urea and other excretory compounds. This distinct evidence of increased tissue metamorphosis, and the undoubted competence of this to cause increased production of heat, are the foundations on which this theory of fever rests. If this expressed the whole truth, and if fever simply consisted in increased heat due to increased tissue metamorphosis, the amount of febrile disturbance should bear a direct relation to the extent of the tissue disintegration, and the quantity of excreta eliminated should be directly as the amount of fever. The fact that such is not always the case, and that the amount of urea excreted does not always rise and fall with the rise and fall of the temperature, has cast doubts on the accuracy of this theory, and led observers to seek for some other explanation of the rise of temperature. And the more one studies the phenomena of fever at the bedside, the more apparent does it become that increased tissue metabolism is not enough to explain them all.

In 1863 Traube advanced the hypothesis that the rise of temperature was due to retention of heat consequent on contraction of the minute arteries. Liebermeister and Leyden demonstrated the inaccuracy of Traube's hypothesis, and by a series of careful observations showed that the febrile body does give off more heat than the non-febrile—a fact already made familiar to every clinical observer by the greater sense of heat felt by the hand placed under the bed-clothes of a patient suffering from fever, as compared with that felt in the case of the non-febrile. Ten years later Senator revived Traube's hypothesis in a modified form. He supposed that there are periodic diminutions of loss of heat, together with a constant, though not great, increase of heat production. But this is mere hypothesis, and is opposed to the facts observed by Liebermeister and Leyden.

There is really no valid reason for supposing that during fever the mutual relation of heat-production and heat-elimination is materially altered. That there is increased production of heat is undoubted; but a careful consideration of the facts with which we have to deal shows that

increased production is met by increased elimination. The range of the temperature in fever has its limits, just as that of health has; the range is wider and more variable, it is true, but still it has its recognised limits. It could not be so limited were the increased production of heat which causes the rise not met by increased elimination.

In health an adult produces in half an hour heat enough to raise the temperature of his body 1° C. Were heat to go on being formed uninterruptedly at this rate, without any elimination, the body would rapidly become very hot, and would reach the boiling-point in thirty-six hours.[1] As it is, the heat does not exceed 98·4°. In fever the amount of heat produced is much greater. Were this increased production to go on with only the normal elimination of health, the range of febrile temperature would have no limits—the temperature would go on rising till it reached a point which was incompatible with the continuance of life. As it is, the temperature in fever rarely reaches 106° F., and the immense majority of fever patients recover. In typhus fever, for example, the maximum temperature is reached by the fifth or sixth day, but the fever goes on for a week or ten days more, all the symptoms increasing in severity; but in very few cases is a higher temperature noted during the second week than was observed before the completion of the first, and yet all that time there is marked wasting of the nitrogenous tissues and increased elimination of urea. The fever process, with its increased metamorphosis and increased heat production, continues in full swing, but the temperature does not rise—clearly showing that there is no accumulation of heat, and that increased production is met by increased elimination. In typhoid fever the same thing is observed: by the tenth day, or even earlier, the temperature generally reaches a height which is not exceeded during theremaining course of the fever; and an attack of typhoid may go on for three, four, or five weeks without having a higher temperature than was noted at the end of the first: clear evidence that the increased

[1] Landois, *Physiology*, p. 445.

formation of heat, which keeps the temperature up, is counterbalanced by increased elimination. Why is this? Why should the temperature rise rapidly during the first few days and not go on rising?

The stage of invasion of a febrile attack is that at which the first symptoms of the action of the poison on the system are felt. The earliest indication of this action is a feeling of cold and misery—a desire to hug the fire. The cause of this is contraction of the minute arteries of the skin. The feeling of cold to which this contraction gives rise is a mere subjective sensation; at the time at which it is felt the temperature is really above the normal—may be, several degrees. Besides this subjective sensation, another result of this spasm of the minute arteries of the skin, that which concerns us at present, is decreased elimination of heat. It is by the skin that heat is normally eliminated; contraction of the cuticular arteries, by diminishing the flow of blood to the surface, produces a corresponding and consequent decrease in heat elimination. While the condition of the cuticular vessels thus interferes with the free elimination of heat, the fever-producing cause is at work in the system, causing heat to be produced there in more than normal amount. The inevitable result is the undue accumulation of heat in the system and a rise of temperature.

This is what takes place during the early days of a febrile attack. In the course of a few days the spasm of the minute arteries passes off, the blood again flows freely through them, the heat-eliminating function of the skin is thus restored, and keeping pace with heat production, prevents a further rise of temperature. Thus is to be explained the fact that in typhus fever the temperature reaches its maximum by the fifth or sixth day, rising little, if at all, after that time. It rises up to that point because there is increased formation of heat, and because the condition of the skin renders impossible a corresponding increase in elimination; it ceases to rise after that time, when the blood again circulates freely through the skin—not because the fever-producing cause has ceased to act, but

because the mutual and normally counterbalancing relations of production and elimination are restored, and increased production is met by increased elimination.

Taking this view of the nature of heat—regarding it as an excretory product requiring to be eliminated—it is evident that increased formation of heat must give rise to increased elimination so long as the skin can perform its functions. Increased formation of any excretory product leads to stimulation and increased activity of the organ by which it is eliminated. Urea is the natural stimulant to the kidneys, and its injection into the circulation gives rise to increased activity of these organs and an increased flow of urine. Carbonic acid excites the respiratory centre, and its increase in the blood causes increased activity of respiration. In the same way increased formation of heat gives rise to increased activity of the heat-eliminating function of the skin; hence it is that before an attack of fever has lasted many days increased formation of heat is balanced by increased elimination, and no further rise takes place, though the fever process continues unabated while the fever-producing cause continues in operation.

Such are the facts. During the continuance of the febrile process there is increased tissue disintegration and consequent increased formation and elimination of the products of such disintegration. The chief of these are urea, carbonic acid, and heat. The so-called combustion theory is simply an exposition of these facts. It is not a theory of fever in the sense of being an explanation of the mode of production of the febrile state; it is merely an attempt to explain one of the phenomena of that state—increased body heat. But a theory of fever to be satisfactory must not only tell us what are the essential phenomena of the febrile process; it must tell us also how the process is originated. If the first step in the production of fever be increased tissue-change, the first requisite to a satisfactory theory of fever is that it should account for this change; this the combustion theory as hitherto expounded fails to do; it gives a reasonable explanation of the leading phenomenon of fever—rise of temperature; but offers no expla-

nation of what, according to this theory, is the cause of this rise, and therefore a prior step in the production of fever—increased tissue-change. We accept the combustion as a fact, but in accepting it we ask for an explanation of its occurrence. We see that the fire is burning, and we recognise the results of the combustion; but we want to know how it originated, and who applied the match that set it a-going. This manifest shortcoming of the combustion theory did not escape the observation of even those who are its chief exponents. To his definition of fever, that it 'consists essentially in elevation of temperature, which must arise from an increased consumption of tissue,' Virchow adds the rider that this increased consumption 'appears to have its immediate cause in alterations of the nervous system.' But to refer it to changes in the nervous system is only to remove the difficulty one step back: What is the change in the nervous system, and how is it brought about?

It has been suggested by Dr. Ord [1] that the rise of temperature in fever may be partly due 'to the persistence in the form of heat of energy which should have taken another form.' In fever, tissue-formation is practically in abeyance, and his suggestion is that, as in health the process of tissue-building uses up heat, its cessation leads to the liberation of heat enough to raise the temperature of the body. But does the process of tissue-building use up heat? In support of his assumption that it does so Dr. Ord adduces no evidence, and frankly admits that there is none. It is contrary to all physiological law to assume that a product of retrograde tissue metamorphosis, an excretory product, as heat undoubtedly is, should be freely used in tissue formation. The position is essentially and physiologically unsound; and Dr. Ord's suggestion that by the cessation of the processes of tissue-formation heat is 'left to run wild' cannot but be regarded as an exaggerated and inaccurate estimate of anything that can possibly take place in the way of heat liberation. Heat is produced during tissue-disintegration: but formation necessarily precedes disintegra-

[1] *Brit. Med. Journal*, vol. ii. 1885.

tion. The cessation of tissue-formation could not lead to the liberation of heat, for the very simple reason that the heat has not yet been formed. Ord's observations on the relative temperatures of growing and ripe cucumbers are beside the mark. We are dealing with animal heat, and even in this the question for consideration is not so much whether heat may be absorbed, but *whether during tissue-formation it is absorbed in quantity sufficient to lower the temperature of the whole body several degrees.* If there is not absorbed during tissue-formation enough heat to lower the temperature several degrees, there cannot, when tissue-formation ceases, be liberated enough to raise it several degrees. But even the acceptance of Dr. Ord's hypothesis would not materially better our position so far as our knowledge of the causation of fever is concerned. 'Rise of temperature,' says Dr. Ord, 'results partly from the cessation of tissue-formation.' But why does tissue-formation cease?

Dr. Ord's hypothesis is based on an unsound physiological assumption. Heat is essentially excretory in nature; and the more we keep this physiological fact before us in investigating the phenomena of the febrile state, the less liable shall we be to fall into error, and the more likely to interpret aright the complex and varied phenomena which go to constitute that state. Dr. Ord's hypothesis, though it cannot be accepted as tenable, or as affording any relief to the difficulties by which we are beset, is, nevertheless, an expression of the existence of these difficulties, and of the fact that there is much in the phenomena of the febrile state which the combustion theory does not suffice to explain. It is a call for more light.

Increased body heat occurs in connection with so many different diseases, and is symptomatic of so many different morbid conditions, that it is not unlikely that it may be brought about in more than one way, and that the 'fever' which we note in one disease is not necessarily produced in the same way as that found in another. Since Virchow propounded his theory, the subject of thermogenesis has had much light thrown upon it by both physiological research and clinical observation. Physiological research has tended

to show that the nervous system exercises a great influence over heat production. Clinical observation has tended to confirm this view.

The nature of this influence is the special point which has to be determined. The weak point in the combustion theory of fever is that, while recognising, and indeed taking its stand upon, the physiological fact that, as heat is a normal product of tissue metabolism, increased formation of heat must be due to increased metabolism—while recognising this, it takes no cognisance of the equally important physiological fact that tissue metabolism is presided over and kept within due bounds by the inhibiting influence of the nervous centres. In controlling metabolism these centres necessarily control heat production. Such being the case, it is evident that increased metabolism, and therefore increased heat, may result from defective control, as well as from increased stimulation of that process.

We thus have two theories of fever to consider: first, that according to which the rise of temperature results from increased activity of the process by which heat is naturally formed; second, that according to which the rise of temperature is due to impairment of that inhibitory force by which the heat-producing process is kept within normal physiological bounds. The first theory we shall refer to as the *metabolic*, the second as the *neurotic*.

These two theories are not antagonistic. Each is complete in itself; and the acceptance of the one does not necessarily mean the rejection of the other.

Before we proceed to apply these theories to the explanation of particular forms of fever, it is essential that we should distinctly understand what is meant by the metabolic and what by the neurotic theory of fever.

There are maladies characterised by increased body heat in which the rise of temperature is due to increased tissue metabolism. There are other maladies in which increased body heat is equally marked, but in which the rise of temperature as clearly results from disturbance of the nervous centres. To the former the metabolic theory applies, to the latter the neurotic. Disturbance of nerve

centres in the former does not make the pyrexia neurotic, if it is directly due to increased activity of tissue metabolism. Increased tissue waste in the latter does not make the fever the less neurotic in origin if its primary cause is disturbance of the nerve centres.

It will lead to a clearer understanding of the whole subject if we take the neurotic theory first.

THE NEUROTIC THEORY OF FEVER.

It is since Virchow's theory was propounded that the thermometer has come into general use as a means of clinical research. By its aid we have not only acquired a more accurate knowledge of the range of temperature in ordinary febrile and inflammatory ailments, but have also gained much information regarding the clinical history of other morbid conditions. The most noticeable of these results, so far as our present inquiry is concerned, is, first, the recognition of the condition to which the term 'hyperpyrexia' has been applied; and, second, the recognition of the fact that non-inflammatory lesions of the nervous centres may cause a considerable increase of body heat.

In ordinary febrile ailments the temperature rarely reaches 106° F., and 105° F. is looked upon as very high. Hyperpyrexia essentially consists (1) in a temperature which runs up, generally very quickly, to 107°, 108°, 109°, 110°, or even higher; and (2) in the coincident development of alarming nervous symptoms. Hyperpyrexia is not a disease *per se*, but an incident occurring in the course of other ailments. The recognition of this condition, of the circumstances under which it arises, and of the phenomena which go to constitute it, has done much to shake confidence in the combustion theory of fever; and no wonder, for it is apparent that, though that theory of fever affords a fairly adequate explanation of the rise of temperature which occurs in ordinary pyrexia, it is quite incapable of explaining the condition which has to be dealt with in hyperpyrexia. The rapidity with which the temperature attains such a height, the absence of the other evidences of such increased tissue-disintegration as should,

on this view, accompany so great a rise, and the fact that hyperpyrexia is comparatively rare even in those fevers in which the evidence of increased tissue-disintegration is most pronounced, show that the combustion theory of pyrexia does not suffice to explain the phenomena of hyperpyrexia.

Pyrexia and hyperpyrexia have hitherto been linked together clinically and pathologically, and looked upon as different degrees of the same condition, allied both in nature and causation. The inadequacy of the combustion theory to explain the occurrence of hyperpyrexia has materially weakened its foundations as a theory of pyrexia; and the necessity for finding some other explanation of the very high temperature of hyperpyrexia has led to the enunciation of new views as to the causation of the more ordinary temperature of pyrexia.

But it is by no means certain that we are right in thus linking these two conditions so closely together, and in looking for one common explanation of both. Their clinical histories are so distinct, and the circumstances under which each occurs so different, that we are scarcely warranted in assuming similarity of causation. Were hyperpyrexia merely an exaggeration of pyrexia, and produced by the same agency, we should find pyrexia running into hyperpyrexia much more frequently than it does, and hyperpyrexia would be most common in ailments in which pyrexia is most pronounced and most a source of danger. Typhus, typhoid, relapsing fever, cerebro-spinal fever, scarlet fever, measles, pneumonia, peritonitis, those diseases in which pyrexia is most pronounced, prominent, and prolonged, are the ones in which hyperpyrexia would be most common were this view of its nature correct. But it is comparatively rare in these maladies. The physician finds it not in connection with the continued fevers, or severe inflammations, but in heat apoplexy, in cerebral hæmorrhage, and in those cases of acute rheumatism which are accompanied by cerebral symptoms—what used to be called 'cerebral rheumatism.' The surgeon finds it not in long-continued or severe inflammations of wounds, bones,

veins, &c., but in pyæmia, and in certain injuries of the cervical cord, involving little or no inflammatory disturbance.

One point in the clinical history of hyperpyrexia is specially prominent, the association of the very high temperature with prominent nervous symptoms. This association is all but invariable, and such symptoms are as essential a part of the morbid condition to which we apply the term 'hyperpyrexia,' as is the very high temperature to which it owes its name.

What is the mutual relation of the high temperature and the cerebral disturbance? There are two views on this point: one, that the high temperature causes the nervous symptoms; the other, that the cerebral disturbance is primary, and the high temperature a consequence of it. According to the former view the high temperature of the blood causes disturbance, and ultimately paralysis of the nervous centres.[1] But were this the sequence of events, the prominence of the nervous symptoms would be directly as the height of the temperature, and such symptoms would be most marked in ailments in which the temperature runs highest. But such is not the case. Isolated cases of disease are on record in which very high temperatures have been noted without coincident nervous symptoms. But leaving out of account these rare and exceptional cases, we need only turn to the clinical history of relapsing fever for distinct evidence that high temperatures do not necessarily produce serious disturbance of the nervous centres. In that fever it is not uncommon for the temperature to run up to 106°, 107°, and even 108° without the occurrence of any symptom other than this high temperature to distinguish the cases in which it occurs from those in which the temperature never exceeds 103° or 104°. 'A circumstance of some importance in the pathology of pyrexia,' says Murchison, 'is the fact, conclusively established by many independent observers, that these high temperatures in relapsing fever entail little or no danger to the patient, and do not produce serious cerebral symptoms.'

It is evident that the view that the nervous symptoms

[1] Liebermeister, *Deutsch. Arch. für Klin. Med.* vol. i. 1856.

are caused by the high temperature lacks the clinical support which would commend it to our reason.

Experimental evidence seems to afford to it more support. The chief evidence of this kind is that adduced by Wood.[1] He placed rabbits, cats, and dogs in a box, and raised the temperature of this to 120° to 130°, and found that in animals so exposed the temperature rapidly rose, and that by the time it reached eight or ten degrees above the normal the animals died. The experiments were evidently performed with great care, and the results very accurately noted. From these Dr. Wood draws the conclusion that it may be regarded as proven that 'external heat applied to the body of normal animals, including man, so as to elevate the internal temperature, produces derangements of the functions of innervation, of respiration, of circulation, &c., precisely similar to those seen in natural fever, the intensity of the disturbance being directly proportionate to the rise in temperature.' He further adds, no doubt in explanation of his including man in this generalisation, that 'the brain of a man is much more highly organised, and no doubt correspondingly more sensitive, than that of a cat; and if a temperature of 113° F. be fatal to the brain of a cat, whose normal temperature is 102·5°, it seems very certain that the temperature of some cases of insolation (113°) is sufficient in itself to cause death in man, whose normal temperature is 99°.' Much as one admires the patience and skill with which Dr. Wood made his observations, one cannot fail to see that they do not warrant these inferences, and that Dr. Wood has failed to grasp the correct interpretation and bearing of his own facts.

In the first place, there are no grounds for 'including man' in the general inference which he draws. No observations were made on man, and in this matter the results of experiments made on cats and dogs cannot be accepted as applicable to him. Man naturally eliminates through his skin an enormous amount of heat, and possesses a power of accommodating himself to high temperatures,

[1] *Fever: a Study in Morbid and Normal Physiology.* By B. C. Wood, M.A., M.D. Philadelphia: 1880.

which is not possessed by the animals experimented on by Dr. Wood. The temperature which he found proved fatal to cats and dogs is one to which man may be and constantly is exposed, without serious results. Every time we take a Turkish bath we are exposed for a length of time to a higher temperature than that to which Dr. Wood's animals were exposed.

In the second place, it is not an accurate statement of the physiological position to say that, because a man's brain is more highly organised than a cat's, it is correspondingly more sensitive to heat; and that, because the normal temperature of man is 98·5°, a temperature of 113° must be a more serious thing to him than it is to a cat, whose normal temperature is 102·5°. So far as the intellectual faculties are concerned, man's brain is much more highly organised than that of the lower animals; but so far as the functions of organic life are concerned it is not so. What Dr. Wood really found was that, when the bodily temperature of rabbits, cats, and dogs rose 8° or 10° above the normal, the animals died. But a rise of 8° or 10° above the normal produces *per se* no serious symptoms in man, as is evidenced by the frequency with which such a temperature occurs in relapsing fever without the occurrence of any other symptom to distinguish the cases in which it occurs from those in which the temperature is several degrees lower. That is the proper way to put Dr. Wood's facts. The reason why the temperature which he found to be fatal to cats and dogs does not produce serious results in man is that he can naturally bear a much higher temperature than they, and that the surface of his body possesses a heat-eliminating function which is not possessed by that of cats and dogs.

Then, again, I do not think that Dr. Wood has correctly interpreted the mode in which death was produced in his animals. He says that the derangements produced were 'precisely similar to those seen in natural fever, the intensity of the disturbance being directly proportionate to the rise in temperature.' Of course, this disturbance was most pronounced in the animals which died. But when we

come to inquire into their mode of death, we find it stated that in these fatal cases the heart continued to beat for some time after respiration had ceased. Now, there is no form of fever in which death is ever brought about in that way. In fever death results either from asthenia or coma—cessation of cardiac or cessation of cerebral function; but in Dr. Wood's animals it was brought about by arrest of pulmonary function. And it is not difficult to say why this should have been their mode of death. Man eliminates heat by the skin; the animals experimented on by Dr. Wood eliminate it by the lungs. Breathing as they did in the hot box an atmosphere with a temperature many degrees above that of their blood, it was impossible for them to throw off heat; in such an atmosphere they could not eliminate heat any more than they could eliminate carbonic acid in an atmosphere charged with that gas; heat therefore accumulated in the system. The result of the accumulation in the system of any excretory product is, first, stimulation, and ultimately, if the accumulation be excessive, arrest of the functional activity of the organ by which it is normally eliminated. Accumulation of heat in the blood of Dr. Wood's animals thus led to arrest of pulmonary function, much in the same way that accumulation of carbonic acid in their blood would have done. It was not the heat they took in, but the heat which they failed to give off, that killed them. That was how and why his animals died. But that is a result which could not be produced in man by a like agency, simply because he eliminates heat through his skin. He might die from too great heat, but death would not be brought about by arrest of pulmonary function.

Moreover, there is another practical and very important point in connection with Dr. Wood's investigation which is not altogether to be lost sight of. In his animals heat was applied artificially; by this they were heated up, and the sole question for consideration is the action of this heat on their economy; but in fever and hyperpyrexia there is no artificial heat, and the question at issue is not only the action of the high temperature, but also its mode of pro-

duction—not only what does the heat do, but how does it come to be there. On this, the main question which has to be considered in dealing with this subject of the hyperpyretic state as it occurs in man, the experiments referred to throw no light.

But it is incumbent upon us to explain the occurrence of the high temperature, as well as the nervous symptoms; and no view of the mode of production of the condition to which we apply the term 'hyperpyrexia' can be regarded as satisfactory which does not explain one of its most prominent and striking features—that from which it takes its name. But on the view that the high temperature is primary, how are we to do so?

It is evident that neither the clinical nor the experimental evidence favours the view that the high temperature is the cause of the nervous symptoms. The alternative view, that the high temperature is secondary to disturbance of the nervous centres, has much more to commend it.

The constancy with which, under the most diverse external conditions—in the Arctic cold as in the heat of the tropics—the temperature of the human body remains at 98·4°, has led physiologists to look beyond the conditions of tissue change and surface transpiration, and to regard a dominating influence seated in the nervous centres as essential to the explanation of the phenomena which have to be considered. Some physiologists have indeed gone so far as to endeavour to define the exact position of a thermic centre.[1] Though there is not evidence to warrant the localisation of the function in any one part of the nervous system, there is much evidence to show that that system does exercise a powerful influence over the temperature of the body. The most important of this evidence is clinical. In 1837, Sir Benjamin Brodie drew attention to the fact that injury to the upper part of the cord was, under certain

[1] 'The theory that teaches the existence of a nerve centre in the pons or in the brain above it, which by a direct action inhibits the production of animal heat, seems to be most in accord with all the evidence bearing upon it, and I am disposed to adopt it as at least probable.' (Wood, *op. cit.*)

circumstances, followed by a great rise in the temperature of the body. The accuracy of this observation has been amply confirmed, and sudden and great rise of body heat has come to be regarded as a not uncommon result of injuries affecting the cervical column.[1]

Injuries of the cervical cord are not the only lesions of the nervous centres in which alterations of temperature are noted. One of the many important results which have accrued from the use of the clinical thermometer is the discovery of the fact that non-inflammatory lesions of the brain—hæmorrhage, embolism, tumour—are frequently followed by a rise in the temperature of the body. The subject is one which has come into existence only since the thermometer came into general use; its literature is, therefore, not extensive; but a sufficient number of observations have been made to demonstrate that non-inflammatory lesions of the brain frequently cause a rise of temperature such as does not result from similar lesions in any other organ.

Charcot[2] divides the apoplectic state resulting from hæmorrhage or from cerebral softening into three periods, according to the modifications of temperature: in the first, comprising the first few hours immediately following the attack, the temperature falls below the normal; in the second, which lasts a variable number of days, it varies from 99° to 100°; in the third, which terminates necessarily and speedily in death, it runs up to 102°, 104°, and even 106°. Bourneville[3] divides it into four: (1) the initial lowering of the temperature, (2) the stationary period, (3) the ascending period, and (4) the terminal temperature. The first three are the same as Charcot's. The fourth, which is really the maximum point of the third, is added to indicate that the ascending period does not always stop short at the point noted by Charcot, but that *at the*

[1] For an account of this subject the reader is referred to Mr. Jacobson's article in Holmes's *System of Surgery*, 3rd edition, vol. i. p. 654.

[2] *Leçons cliniques sur les Maladies des Vieillards*, 1869.

[3] *Etudes cliniques et thermométriques sur les Maladies du Système Nerveux*, 1872.

instant of death or some minutes after, there takes place in some cases a very remarkable rise. M. Bourneville gives a table of seventeen cases, eight of which were observed by himself, in which the average temperature a short time before or after death was nearly 107°, while in eight of the seventeen it exceeded 108°. The initial lowering of the temperature is no doubt the result of shock. The second or stationary period is sometimes altogether absent, and after the initial lowering has passed off there may be noted only the rapid rise of temperature of the third and fourth. This stationary period is met with chiefly in cases in which the clot is comparatively small, and in which the ventricles are not injured. Should recovery take place, the stationary period is succeeded by a return of the temperature to the normal standard. Should the case tend to a fatal result, the second period runs into the third, and the temperature rapidly rises. A rising temperature, therefore, indicates a speedily fatal termination.

Since Bourneville's cases were published similar ones have been recorded by other observers; the accuracy of his statements has been amply confirmed, and a rise of temperature has come to be regarded as a common result of cerebral hæmorrhage. But hæmorrhage is not the only form of cerebral lesion in which such alteration of the body heat is noted. The same change has been found to take place in tumours and various other non-inflammatory lesions of the nervous centres.

These clinical facts afford distinct evidence that injuries and non-inflammatory lesions of certain parts of the nervous centres cause a rise in the temperature of the body as great as that noted in inflammatory and febrile ailments. That such lesions give rise to such results shows as clearly as evidence can that the nervous system exercises a marked influence over the body heat.

So far as our present inquiry is concerned—so far, that is, as concerns the theory of fever—the exact location, or even the existence of a localised thermic centre, is not a matter of importance: the important thing is that we should recognise that the nervous centres exercise a direct

and dominant influence over the body heat, and that rise of temperature may be directly due to disturbance affecting them. The acquisition of such knowledge could not fail to materially influence our views as to the causation of fever. If injuries affecting the nervous centres are capable of causing a rise in the body heat, may not even the preternatural heat of ordinary febrile ailments be directly due to the disturbing action on these centres of the so-called fever poison? Such a question was bound to arise so soon as the full bearings of the facts, physiological and pathological, which have been related, were recognised. The necessary outcome of the recognition of the heat-controlling influence of the nervous centres was a 'neurotic' theory of fever. And no time was lost in enunciating it: for in the same volume in which his experiments are related, Wood[1] starts this theory: 'Granting,' he says, 'the existence of a fever centre in the nervous system, the laws of life teach us that there must be poisons capable of acting upon it directly, so as to produce fever. Such a fever would certainly be neurotic, although produced through the blood, the vital fluid acting simply as a common carrier. With this understanding of the terms, distinctly clear proof is at present wanting that the fever even of pyæmia, of the exanthemata, or of any so-called blood poisoning is strictly hæmic, since such toxic fever may be due to an action of the poison upon the central nervous system.' This neurotic theory has in a modified form been ably advocated by Hale White, who believes that 'in specific fevers, inflammations, traumatic and urethral fevers, the rise of temperature is due to peripheral stimulation of afferent nerves reflexly affecting the calorific centre.'[2]

Still more recently the neurotic theory has received the support of Dr. Macalister, who believes 'that all fever is due to an action on the central nervous system.' He regards 'the thermal nervous system as having three parts, the thermotaxic or adjusting, the thermogenic or producing, and the thermolytic or discharging mechanism. Disorder of the first implies irregularity of temperature only; dis-

[1] *Op. cit.* p. 245. [2] *Practitioner*, Jan. 1886.

order of the first and second implies, in general, heightened temperature and increased body heat—that is, ordinary fever; disorder of the first, second, and third implies, in general, hyperpyrexia, dangerous increase of heat, and steadily rising temperature.' Dr. Macalister has studied the subject solely from the physiological side, and rather takes credit to himself for ignoring in his study of the subject the question of the etiology of fever. But the question is not a physiological one, and cannot be studied solely from a physiological standpoint. The study of fever is essentially clinical and pathological, and to ignore the question of etiology in the study of a condition which is common to so many different pathological states, is deliberately to exclude from consideration an essential part of the whole question.

From a physiological point of view, Dr. Macalister's essay is an admirable exposition of the views of those who advocate an exclusive neurotic theory in explanation of all forms of fever. But the question is one in which the last word must rest, not with the physiologist, but with the physician and the pathologist. They are grateful to the physiologist for the help he gives, but they take up the question where he leaves it, and carry it into their own domain. A theory of fever must accord with physiological knowledge; but the primary and essential condition of its existence is that it should give, not only a physiological explanation of the increased body heat, but likewise a satisfactory explanation of the origin, course, and clinical features of the maladies in connection with which this increased heat occurs.

Fever, says Dr. Macalister, is due to disorder of the thermal nervous system. Very good, says the physician, but how is this disorder brought about? I want to know not only wherein fever essentially consists, but also how it and all its attendant phenomena are produced. Why does the poison of scarlatina give rise not only to the disturbance of the thermal nervous system to which you refer, but also to the sore-throat, the rash, and the other symptoms associated with that disturbance? Why does the poison of

measles produce a like disturbance of the thermal nervous system, and a totally different set of phenomena to those noted in scarlatina? Why, in short, does each of the specific fevers have its own specific features and lesions? Again, why does the fever of pneumonia last only a week, that of typhus two weeks, and that of typhoid fever three? These questions cannot be ignored; they must be answered.

The pathogenesis of fever cannot be considered apart from the pathogenesis of the maladies in which it occurs, and of which it is only one of many symptoms; and these maladies vary so much in nature that it is extremely unlikely that any one theory of fever should be applicable to all. Moreover, though a nervous centre is an essential part of the thermal apparatus, it is not the whole of it; and the advocates of an exclusively neurotic theory have probably been led astray by concentrating their attention on the central nervous part of this apparatus, to the exclusion of other parts equally essential to the phenomena of heat production and heat elimination.

The thermal apparatus consists of various parts, and is distributed over the whole body, more or less. First, there is the dominating central power in the nervous centres. Such a central power must be connected with the parts of the body in which heat is produced, for without this it could exercise no influence over heat production. It must equally be in communication with the parts of the body by which heat is eliminated, for without this it could exercise no control over heat elimination. The nervous centres could no more control and regulate the production and elimination of heat, without a connection with the seats of heat production and heat elimination, than the vaso-motor centre could control the circulation through the minute arteries without being in communication with the muscular coats of these vessels. The only way in which such a connection could be established is by means of nerves, for nerves are the sole media by which impressions are conveyed to and from nerve centres. The parts which go to form the thermal apparatus, therefore, are: 1. The tissues in which heat is formed. 2. The surface from which heat is eliminated.

3. A central controlling power in the nervous centres. 4. Nerves connecting this with the heat-forming parts of the body. 5. Nerves connecting it with the heat-eliminating surface. The harmonious working of these different parts of the thermal apparatus gives rise to the phenomena of thermogenesis; and the general result is a persistent temperature of 98·4°. Interruption of this harmony causes the temperature to rise or fall. Fall of temperature is due either to lessened formation or increased elimination of heat. Rise of temperature is produced either by increased formation or decreased elimination.

Rise of temperature due to increased formation may be brought about in two ways: by direct stimulation of the processes by which heat is formed, or by diminished activity of that by which heat formation is inhibited, or kept within due bounds.

Rise of temperature due to direct stimulation of the process by which heat is formed must be brought about by some agency which increases tissue metabolism. Heat is an excretory product, a result of retrograde tissue change, and cannot be produced apart from that change. To say that heat could be directly brought about by stimulation of a heat-producing centre, without increased tissue change, would be to place heat as a product on the same level and in the same category as volition and emotion, which is absurd. Increased heat due to direct stimulation of the heat-producing process must be due to the operation of some agency capable of causing increased activity of tissue metabolism. We can no more have increased formation of heat without increased activity of the processes during which heat is formed, than we can have increased formation of urea or increased formation of carbonic acid without increased activity of the processes during which they are formed. That the continuance of normal tissue metabolism is dependent on influences conveyed to the tissues by the trophic nerves is undoubted. And it is quite conceivable that stimulation applied to the centres whence these trophic nerves proceed, might, by causing increased activity of tissue metabolism, give rise to increased production of heat.

The experiments of Messrs. Aronsohn and Sachs,[1] in which electrical stimulation of a particular portion of the corpus striatum produced a rise of temperature varying from $2\frac{1}{2}$ to $4\frac{1}{2}$ degrees Fahrenheit, would seem to indicate that fever may be produced by direct stimulation of a certain portion of the nervous centres : and the possibility of such a result must be kept before us in investigating the mode of production of the febrile phenomena of any given disease.

But equally must it be borne in mind that such a result could be brought about only by causing increased activity of the metabolic changes by which heat is formed in the tissues. Such a nerve centre can be only one portion of the heat-producing apparatus, and it is quite possible that stimulation applied to other parts of this apparatus might cause the temperature to rise without primary stimulation of a nervous centre.

Besides dominating heat production, the nervous centres also control heat inhibition, and by so doing keep the temperature at the normal standard in health ; and in disease prevent it from passing due bounds.

Inhibition restrains and regulates functional activity, as the reins restrain and regulate the pace of a spirited horse. Slacken the reins, and he hastens his pace; let them go, and he is off at the gallop. Inhibition is an active, not a passive agency, and is in constant operation. This is well exemplified by the action of the vagus on the heart; stimulation of that nerve slows the heart's action, and, if the stimulus be strong enough, may arrest it altogether, the arrest taking place in diastole. But the nervous system which supplies this inhibiting force supplies also another, which, reaching the heart by another channel, has exactly the opposite effect; it stimulates the heart to increased activity. These two forces are in constant operation, and so counterbalance each other that the heart is normally kept beating at the rate of about seventy a minute.

There is no organ whose normal amount of work repre-

[1] *Die Beziehungen des Gehirns zur Körperwärme und zum Fieber*, Pflüger's *Archiv*, Bd. xxxvii. Oct. 1885.

sents the full measure of its capacity; there is no function whose normal state of activity represents the full possibilities of its performance. Each is restrained and kept within physiological bounds by the inhibiting action of the nervous system. Tissue metabolism is no exception to the rule. Normally, tissue formation and tissue disintegration counterbalance each other. But let the reins be slackened, let inhibition of metabolism be impaired, metabolism is necessarily increased, and pyrexia results. Let the reins be cast loose, let inhibition be paralysed, and metabolism, freed from control, is off at the gallop, and hyperpyrexia results. Hyperpyrexia may be defined as paralysis of inhibition of metabolism; paralysis of heat inhibition being only part of the process.

The clearest and most undoubted cases of neurotic pyrexia are those in which the rise of temperature succeeds, and is symptomatic of, a non-inflammatory lesion of the nervous centres. Examples of such pyrexia we have in that which accompanies cerebral hæmorrhage, tumour of the brain, and injuries of the cervical cord. No other explanation can be given of the rise of temperature in these cases except that offered by the neurotic theory. The question is, How does the nervous lesion lead to such a result?

It is impossible to regard the results of such lesions, consisting as they essentially do of pressure upon, or laceration of, a portion of the nervous centres, as other than paralytic in nature. The effect of all such mechanical lesions is not to increase, but to impair or abolish, function—to produce more or less paralysis. The only way in which a destructive and non-inflammatory lesion could cause temperature to rise is by impairing that function which normally prevents it from rising—in other words, by impairing heat inhibition. Rise of temperature thus produced will vary according to the extent of the lesion; in slighter injuries there may be no serious damage to the nervous centres, and no greater rise of temperature than is noted in cases of cerebral hæmorrhage in which the sanguineous effusion is small and does not open into the ven-

tricles. In more extensive lesions, in which these centres are more seriously damaged (as in severe cases of cerebral hæmorrhage in which the effusion is more extensive and tears its way into the ventricles), the temperature rises rapidly and to a much higher point; while the highest temperature of all is noted in cases of crushing of the cord, in which the heat-forming parts of the body may have their connection with the heat-inhibiting centres cut off more completely than is likely to be the case in any intra-cranial lesion.

Admitting that the nervous system possesses the power to control and limit heat formation, and prevent undue rise of temperature, we have no difficulty in the maladies and injuries to which reference has been made, in attributing the increased body heat to interference with that function. The temperature rises because the reins are slackened. The sequence of events seems to admit of no other explanation. Carrying on this line of argument, we cannot fail to see, not only that the rise of temperature thus induced must be directly as the extent to which heat inhibition is impaired, but that paralysis of this function, by abolishing inhibition and leaving heat production in uncontrolled possession of the field, must lead to hyperpyrexia. And the more we consider the pathogenesis of febrile heat, the more apparent does it become that impairment of inhibition is a much more likely cause of hyperpyrexia than is direct stimulation of heat production. Heat inhibition remaining unimpaired, tissue metabolism could not cause those very high temperatures which characterise some cases of hyperpyrexia. Heat inhibition being paralysed, the temperature cannot fail to rise, and to rise rapidly, so long as tissue metabolism and heat production continue.

All cases of hyperpyrexia we, therefore, regard as of neurotic origin—as due to some cause which exercises a paralysing influence on the heat-inhibiting function. Pyrexia may result either from increased production or from defective inhibition, but hyperpyrexia is due only to defective inhibition.

In the cases hitherto instanced there has been a direct

lesion of the nervous centres to explain the paralysis of inhibition and consequent rise of temperature. Other cases there are, however, in which the evidence of paralysis of that function is equally marked, in which hyperpyrexia is pronounced, but in which the sequence of events by which it is brought about is not so apparent.

But mechanical lesions and organic disease are not the only causes of paralysis. Paralytic symptoms, often not much less marked than those which follow organic lesions of the nervous centres, occur in hysteria; we recognise them, too, in connection with gout and disease of the kidney, and we constantly find them occur as a sequela of diphtheria. Excessive functional use may also lead to impairment and partial paralysis of a part, as in the case of scriveners' palsy, and in the tetanising of a muscle.

With distinct evidence that paralysis of certain parts of the body may occur without any organic lesion to account for it, there is no ground for claiming for the heat inhibiting part of the nervous centres immunity from such disturbance; and there is much evidence to show that it enjoys no such immunity. With that evidence we have now to deal. We shall consider it as it presents itself in hysterical pyrexia, in the hyperpyrexia of heat apoplexy, and in that of acute rheumatism.

Hysterical pyrexia and hyperpyrexia.—The name here expresses all that we really know about this condition. Cases are on record in which hysterical symptoms have been accompanied by a rise of temperature for which no explanation could be found. With distinct evidence that hysteria may cause paralysis of a limb, of the vocal cords, and of the bladder, we need have no difficulty in admitting the possibility of its causing impairment and even paralysis of heat inhibition. The essential symptom of such a condition would be great rise of temperature.

Heat apoplexy results from exposure to heat. In the fully developed disease there is complete insensibility with a very high temperature; but the onset of this alarming condition is generally preceded for some days by headache, giddiness, restlessness, or other evidence of disturbance of

the nervous system. That continued exposure to a high temperature is likely, in a native of a temperate climate unaccustomed to such exposure, to cause disturbance of the thermal apparatus there can be no doubt; and a brief consideration of the mode in which this disturbance is likely to be brought about makes it apparent that such exposure, if sufficiently great or long continued, may cause paralysis of the heat-inhibiting centre, and consequent great rise of temperature. Heat is an excretory product requiring to be eliminated; its chief seat of formation is the muscles; its main channel of elimination is the skin ; a high temperature of the atmosphere necessarily interferes with such elimination, because in such an atmosphere heat cannot readily be thrown off. Heat elimination being thus checked, and heat production continuing as usual, heat must accumulate in the system, unless some agency steps in either to increase elimination or diminish formation. Under ordinary circumstances nature provides the remedy; for the same atmosphere which makes heat elimination difficult causes also increased activity of the skin, and so to some extent meets the difficulty which itself creates; while the general influence of residence in a hot climate leads to habits of life which diminish tissue metabolism and heat production : thus the risk of heat accumulation is diminished at both ends. But circumstances every now and then arise which break through these habits. Such circumstances are those which call for exposure and muscular effort during the heat of the day, as in the case of soldiers on the march. Tissue metabolism and heat production are stimulated, while the body is exposed to a temperature which makes impossible a corresponding increase in heat elimination. Under such circumstances, the only way in which the danger attendant on undue accumulation of heat can be warded off is by restraining heat production, and this end can be attained only by increased activity of the heat-inhibiting function. Heat is the natural stimulus of that function, and accumulation of heat in the system naturally excites it to increased activity. But in a tropical climate the call may very readily be beyond its powers: it continues to make the effort and

struggles to keep the temperature down, till over-stimulation leads to exhaustion; its efforts become feebler, and ultimately, paralysed by fatigue, it ceases to act. Thus is removed the last safeguard; heat rapidly accumulates in the system, and heat apoplexy, with its attendant hyperpyrexia, results. What takes place in the thermic centre under such circumstances is the counterpart of what takes place in the respiratory centre when, under allied circumstances, carbonic acid accumulates in the blood. The first effect of increase of carbonic acid in the blood is to stimulate the respiratory centre and cause increased frequency of respiration. If the gas goes on accumulating, that centre begins to show evidence of fatigue, the respirations become slower and more laboured, the interval between them becomes wider, and finally they cease altogether, the heart continuing to beat for some time longer. The cause of their cessation is paralysis of the respiratory centre, induced by accumulation of carbonic acid, the natural stimulus of that centre. In the same way, accumulation of heat in the system causes first stimulation and ultimately paralysis of heat-inhibition; and thus we explain the great rise of temperature in heat apoplexy. Post-mortem examination of fatal cases shows only a tendency to rapid decomposition, a fluid condition of the blood, and more or less congestion of the lungs.

Rheumatic hyperpyrexia.—Every now and then cases of acute rheumatism occur which, after presenting the symptoms of the malady in their ordinary form, suddenly develop alarming nervous symptoms, with a temperature rapidly rising to 108°, 109°, 110°, and even higher, and a tendency to death by coma. How is this great rise of temperature brought about? 1. It might be merely an exaggeration of the ordinary pyrexia of the disease. 2. It might result from a direct paralysing action of the rheumatic poison on the heat-inhibiting centre. 3. It might be produced in the same way as heat apoplexy, by over-stimulation of the inhibitory centre, resulting in paralysis of heat inhibition, and consequent rapid rise of temperature.

A very little consideration suffices to show that the first hypothesis is not adequate. Were the hyperpyrexia of

acute rheumatism merely an exaggeration of the ordinary pyrexia of the disease, cases in which it occurs would be characterised by inordinate severity of the rheumatic symptoms. But such is not the case. In cases which become hyperpyretic the disease up to the onset of the hyperpyrexia presents no unusual features. The temperature, the joint pains, the acid sweats, the heart complications, are all such as are met with daily in ordinary rheumatic attacks; and there is nothing in their symptoms to lead the physician to anticipate so alarming a complication.

The hypothesis that it may result from paralysis of the heat-inhibiting centre consequent on the direct toxic action on that centre of the rheumatic poison, or some product of the rheumatic process, is one regarding which no more can be said than that it is possible. Against it may be adduced the argument that were such the mode of production of rheumatic hyperpyrexia, that condition would arise more frequently than it does. The rheumatic poison and the products of the rheumatic process operate in every case, but hyperpyrexia is of rare occurrence.

The third hypothesis is one for which more may be said, for between heat apoplexy and rheumatic hyperpyrexia there are many points of analogy. The symptoms and clinical features of both are very much alike, and the description of the post-mortem appearances observed in the one serves equally to describe those noted in the other. Treatment, too, is the same in both. The main difference between them is in the circumstances which lead up to their occurrence. With so many points of resemblance between them we cannot but look for a common mode of production, some common pathological bond. The question for consideration is the possibility of the rheumatic process, as it exists in acute rheumatism, producing the same result as we find follow exposure to great heat. This latter acts by over-stimulating, fatiguing, and finally paralysing the thermic inhibitory centre. The question before us, therefore, narrows itself into a consideration of the point as to whether or not over-stimulation and consequent fatigue of the heat-inhibiting centre is a possible result of the process of acute

rheumatism. Wide as is the difference between that process and great heat, and great as seems the improbability of two such different agencies producing the same effect on the system, a careful consideration of the facts nevertheless leads to the conclusion that such result is not impossible. Certain it is that if over-stimulation and consequent fatigue and impairment of heat inhibition could be a result of any fever, rheumatic fever is the one in which it would most likely manifest itself, and that for the following reasons:—

In all fevers the rise of temperature results from increased tissue metamorphosis, as will be presently explained. This is the case in rheumatic fever, as it is in typhus, typhoid, and other fevers. But the circumstances under which that increased metabolism takes place in rheumatic fever are altogether peculiar to itself; and the peculiarity of these circumstances it is which leads up to the phenomenon which we are now considering—the greater tendency to the occurrence of hyperpyretic complication. Rheumatism is essentially a disease of the motor apparatus of the body. Part of this motor apparatus—the muscles—is the chief seat of heat production. The more active the metabolism of the muscles, the greater the amount of potential energy produced. This potential energy may take the form of work or heat. As a matter of fact, it generally assumes the form of work, for it is when muscles are actively contracting that this potential energy is chiefly formed. But if the same metabolic changes which take place in a contracting muscle were to take place in that muscle when quiescent, the potential energy would take the form not of work but of heat. This is what occurs in acute rheumatism. The rheumatic poison causes a general febrile disturbance accompanied by inflammation of the fibrous textures of the large joints. Inflammation of these textures is of course accompanied by increased flow of blood to, and increased metamorphosis in, them. Apart from the muscles with which they are connected, the fibrous tendons and ligaments have no function, no *raison d'être*. So intimately are the muscles and the textures involved in acute rheumatism connected in their function, in their innervation, in their

vaso-motor and blood-supply, and in all that concerns their vital activity, that inflammation of the fibrous textures could not fail to produce in the muscles some degree of the same increased tissue change, the same abnormal metabolism, which is taking place in the fibrous textures as the result of the action of the rheumatic poison. This is not mere hypothesis, for we have distinct tangible evidence that there does occur in acute rheumatism such increased metabolism of muscle as is usually associated with active exercise. This evidence is the persistent presence in the system during the course of that disease of an excess of lactic acid. That acid is a metabolic product of muscle; it is formed in increased quantity during muscular exercise; and its constant presence in excess in the course of acute rheumatism is distinct and clear evidence that that disease has for one of its phenomena increased metabolism of muscle. It is the only form of fever in which such evidence exists. Muscle being the chief seat of the formation of heat, and the metabolism of muscle being the chief source of heat, it follows that the disease in which such metabolism is most active is also that in which most heat will be formed. That disease is acute rheumatism. Theoretically, there is thus reason to believe that heat production is more active in acute rheumatism than in any other disease. There is also practical evidence that such is the case. The natural result of increased formation of heat is its increased elimination. The skin is the channel by which heat is eliminated. We accordingly find that profuse perspiration, the evidence of excessive action of the skin, forms one of the characteristic features of rheumatic fever. It is the only form of fever which is so characterised. Excessive production is thus met by excessive elimination of heat, and no undue rise of temperature occurs.

But another result of such increased activity of the heat-producing process must be stimulation of heat inhibition. The function of the heat-inhibiting centre is to restrain excessive formation of heat—excessive formation of heat is most marked in acute rheumatism; that function is, therefore, likely to be called into more active operation in acute

rheumatism than in any other disease. It might happen, either from want of vigour, or from unusual susceptibility of that centre, aided possibly by more or less failure in the heat-eliminating action of the skin, that heat production was in excess of heat elimination. Under such circumstances heat would accumulate in the system. As a result of this the heat-inhibiting centre would be first stimulated to excessive effort, then fatigued, and finally paralysed, as in heat apoplexy, and hyperpyrexia would result. That is a sequence of events which might occur in any form of fever or in any ailment, accompanied by increased activity of the heat-producing process. The more active that process the more likely is it to happen. Acute rheumatism being the ailment in which heat is most abundantly and rapidly formed, is also the one in which inhibition is most likely to be over-matched. Hyperpyrexia is, therefore, more common in it than in any other form of fever.

Though for convenience' sake we refer to paralysis of heat inhibition as the immediate cause of the very high temperature, it is evident that it is not only heat inhibition, but inhibition of metabolism in general that is paralysed. Hyperpyrexia may, as already stated, be defined as paralysis of inhibition of metabolism—heat inhibition being only part of it. It is not the high temperature that causes the nervous symptoms, but disturbance of the nervous centres that causes the high temperature. In accordance with this we find that, both in heat apoplexy and in rheumatic hyperpyrexia, the occurrence of the high temperature is generally preceded by headache, giddiness, restlessness, or other indication of disturbance of the nervous centres. All Indian authorities refer to these premonitory indications in the case of heat apoplexy. In cases of acute rheumatism which become hyperpyretic, there will generally be found evidence of disturbance of the nervous system preceding the hyperpyrexia; and such disturbance should put us on the watch for graver symptoms.

In the form of neurotic pyrexia which we have been considering, the disturbance which gives rise to it is of central origin. But that is not the only form of neurotic

pyrexia. Another form there is in which it is of peripheral origin—in which the cause which produces the fever acts on the nervous centres not directly, but indirectly through the nerves. This is the form for whose recognition Dr. Hale White has specially pleaded. He has particularly insisted on the point that the rise of temperature noted in the fever which is symptomatic of local inflammation bears no relation to the extent of the inflammatory disturbance. He believes that the tension of the surrounding tissues plays a more important part in the production of the fever than does the amount of inflammation.

It certainly is the case that in abscess the temperature as a rule is highest in cases in which there is pain, and pain in abscess means tension. Dr. White believes that 'the cerebral calorific centres are affected reflexly by the tension of the inflamed parts acting as a stimulant which takes off their normal inhibition.'

It is an interesting corroboration of this view of the mode of production of the fever which accompanies the formation of matter, that in abscess of the brain, abscess involving only the cerebral substance, there is no fever, the temperature being more likely below than above the normal even where the pus is putrid. In any other part of the body the formation of matter is accompanied by rise of temperature; in the brain only does such rise not occur. The only explanation that can be given of this is that the brain is the only part of the body which is not supplied with nerves. Tension there causes stupor and heaviness, and a temperature rather below than above the normal; there is no pain and no fever; the absence of both is probably due to the same cause—the absence of nerves by which alone impressions could be conveyed to nerve centres.

It is evident that the neurotic theory of fever rests on a very adequate basis, and affords a reasonable explanation of the rise of temperature noted in many morbid conditions; and that it gives of the occurrence of the very high temperature of hyperpyrexia an explanation which, if not the only one possible, is at least more satisfactory than that offered by any other theory. But adequate as this theory

is, nay, necessary as it is, to the explanation of the rise of temperature noted in the ailments and morbid conditions to which reference has hitherto been made, we must be careful not to let our advocacy of it carry us too far, or to try to explain by it the rise of temperature of ailments whose pyrexia can be better and more satisfactorily explained on the metabolic theory. The neurotic and the metabolic theories of fever are not antagonistic. Each has its own special sphere of application. But both are essential to the explanation of all the forms of pyrexia which come under our notice. The sphere of application of the neurotic theory we have already indicated. We pass to the consideration of that of the metabolic theory.

THE METABOLIC THEORY OF FEVER.

The maladies to the explanation of whose pyrexia the metabolic theory applies are numerous and important. To consider them all would be impossible here, and would not lead to a clearer understanding than the plan of illustrating this theory by important and typical examples. For this purpose let us take the specific fevers. They are chosen (1) because they are the most important group of febrile diseases to which man is liable; (2) because they are the maladies in which the evidence of increased tissue metabolism is most marked; (3) because the febrile process can be more conveniently studied in them than in any other maladies; and (4) because we know more about the nature of the cause (the specific poison) which gives rise to them than we do about the cause of most other febrile ailments, and can therefore more readily investigate its probable mode of action in the production of febrile disturbance.

The poisons of the specific fevers are reproduced in the system during the course of the diseases to which they give rise. As nothing but an organism ever is reproduced, no other argument is needed to show that these poisons are minute organisms. This view of their nature is the only one which satisfactorily explains the facts of infection. We have now to explain by it the phenomena of the specific fevers as these present themselves at the bedside. It is the reproduction of the poison in the system which causes the whole disturbance. Before it takes place there is no fever; during its continuance fever is the prominent condition with which we have to deal; after its cessation the fever rapidly declines. How does such a result flow from such a cause? How does the propagation of this poison in

the system raise the body heat? It can be only in one of two ways—by impairing heat inhibition, or by stimulating the processes which result in heat production. In favour of the former view, it is difficult to find anything to say except that it is possible. A very little consideration, however, will show that, though not much can be said for this view, a great deal may be said against it. According to this view of the matter, the poisons of the specific fevers exercise for the time a more or less paralysing effect on the heat-inhibiting function—the result of which would be, of course, rise of temperature. But if such were the case, this action ought to be more and more pronounced as the poison which gives rise to it increases in amount in the system, and the temperature should go on rising as the disease advances, getting daily higher and higher, and keeping pace in its rise with the increasing prominence of the other symptoms—wasting, prostration, delirium, &c. It ought, too, to remain high so long as the poison exists in the system. That is what ought to be if the poison exercised a direct toxic action on the heat-inhibiting function. But the facts are quite the reverse. Take typhus and typhoid fever as typical instances. We find that in these fevers the temperature reaches its highest point very early in the disease—maybe even before its characteristic symptoms are fully developed,—and is no higher after two or three weeks of fever than after five or six days of it, though the poison which causes all the disturbance is being largely reproduced during the whole time. Again, it is a fact that in each of the specific fevers the temperature returns to the normal while there is still in the system a large quantity of the poison of the disease, as is abundantly evidenced by the contagiousness of these maladies during the early days of convalescence. Did that poison have a direct paralysing effect on the heat-inhibiting function, and were the rise of temperature due to such an action, the body heat would rise with the increase of the poison, fever would continue so long as that poison existed in any quantity in the system, and the temperature would not fall till it had been eliminated. As it is, the temperature does not rise after the first five or six

days, and there is good reason to believe that the system contains more of the poison at the commencement of defervescence, when the temperature is rapidly falling, than it does during the first few days of the fever, when it is rapidly rising.

The evidence is opposed to the view that the increased body heat of the specific fevers is due to the direct action of the fever poison on the heat-inhibiting function. Indeed, nothing worthy of the name of evidence can be adduced in support of such a view, and there remains for us nothing but to reject it.

It is otherwise with the view which attributes the rise of temperature to increased production of heat.

The factors involved in normal nutrition are the blood, the tissues, and the nervous system. There must be tissues to be nourished, blood to nourish them, and a nervous system exercising those trophic influences which we know to be an essential part of the nutritive process. Derangement of this process implies disturbance in one or more of these factors.

The poisons of the specific fevers produce such derangement; and their action must be primarily on the blood, on the tissues, or on the nervous system. On which is it?

That fever results from a direct action of the fever poison on the central nervous system is the particular form of the neurotic theory to which Virchow, Wood, and Macalister lean. That it results from an indirect action on that centre, consequent on peripheral stimulation, is that which Hale White teaches.

Whichever view we take, it is evident that the disturbing action on the nervous centres would be directly as the amount of fever poison acting on them, that the fever should be more and more pronounced as that poison increased in quantity, and that it should come to an end only when the poisoned is eliminated. That is what would be if the poison acted on the nervous centres. But that is very different from what really occurs.

Taking again the cases of typhus and typhoid fevers, we find that the maximum temperature is reached early

in the disease, that the poison goes on being reproduced in greater and greater quantity, and all the symptoms increase in severity, but without any further rise of temperature. We find, too, that the temperature returns to the normal, and the fever comes to an end, while the system still contains much of the poison which gave rise to the whole disturbance. For these reasons it is not possible for us to accept the view that the rise of temperature in these fevers results from the action of the poison on the nervous centres.

Besides the nervous system, the other factors involved in nutrition are, as already stated, the blood and tissues. If the action of the fever poison is not on the nervous system, it must be on the blood or tissues, or both. That is the point which now presents itself for consideration.

Its consideration cannot be better introduced than by quoting the able criticism made by Sir Wm. Jenner more than thirty years ago, when reviewing the theory advanced by Virchow. As already indicated, the German pathologist assigned the principal part in the production of fever to the nervous system. Commenting on this, Sir Wm. Jenner says: 'We must say that to our mind it appears possible that too little influence has been attributed by the distinguished German pathologist to the blood as the effective agent in the production of the primary molecular changes, and of the symptoms in the earlier and more advanced stages of fever. For whatever evidence speculation or facts may afford of the participation of the nervous system in the lesions of function which give rise to or constitute the appearances or symptoms of fever, equally strong evidence can be offered of the participation of the blood in the production of the earlier and the later phenomena of fever. The fact is admitted to be indisputable that the fever-making cause enters the blood; so that it is certainly *à priori* more probable that a change should be effected in that fluid before any is effected in the nervous system than the reverse. And there can be no doubt that the necessity for a healthy condition of the blood is as essential to the formation of normal secretions as a healthy state of the nervous system.

. . . But while we think there is strong evidence in favour of the primary affection of the blood, and of the widespread and fearfully severe influence on the system generally of the very deep lesion which in many cases we can demonstrate the blood to have experienced, independently of mere admixture of excess of excrementitious matters, we by no means exclude the nervous system or any other part of the body from a share in the production of the symptoms of fever.' (*British and Foreign Medico-Chirurgical Review*, April 1856.)

The view here indicated by Jenner, that the cause which makes the fever is the poison which enters the system from without, that the action of this poison is primarily on the blood, that the earlier and later phenomena of fever are all due to this action, and that no part of the body can be excluded from the effects of such action, is that which we now advocate, aided by all the additional light that has been thrown on the subject by the numerous and important researches which have been made since Jenner wrote these pregnant and far-seeing words.

That it is not the *presence* of the poison in the system, but its *reproduction* there that gives rise to the febrile phenomena, is evidenced, first, by the fact that there is a long period of incubation, of immunity from any apparent action, after the poison has entered the system, and that not till its reproduction has continued for some days is there any evidence of its action ; and second, by the additional fact that the action of the poison ceases, and the fever comes to an end some time before the poison is eliminated from the system. The specific poison of the disease is the cause which gives rise to each of the specific fevers ; that poison must, therefore, be directly or indirectly the cause of the individual phenomena which go to constitute the fever. The question for consideration, therefore, is not the competence of such a cause to produce such a result—for that is demonstrated by the occurrence of the fever—but its mode of action. How does the propagation of the contagium in the system give rise to the thirst, dry skin, quick

pulse, rise of temperature, waste of tissue, and disturbance of the nervous centres characteristic of these maladies?

In investigating the action of ordinary poisonous and medicinal agencies, we have to consider only their action on one or more organs, or on the system generally, and have to deal only with the action of the quantity which has been swallowed. It is otherwise with the poisons of the specific fevers. Here we have to deal with an organism which is reproduced in large quantity in the system, and which in its growth and reproduction consumes the same materials as the tissues themselves. All organisms have a definite action on their environment. This action, in the case of such organisms as those of the specific fevers, essentially consists in the consumption of nitrogen and water. The environment of these organisms is the blood and tissues of the human body. The action of these organisms on the body, therefore, essentially consists in the consumption of its nitrogen and water. As nitrogen and water are the chief elements requisite to the nutrition and building up of the tissues, and as these tissues are dependent for their continued vitality and functional activity on a due supply of nitrogen and water, it is evident that the growth and reproduction in them of millions of organisms which consume these elements must have a seriously disturbing action on the whole system. All the essential phenomena of the specific fevers are attributable to this action—to the consumption by the poisons of these diseases of nitrogen and water destined for the nutrition of the tissues.

The essential phenomena of fever are:—

1. Wasting of the nitrogenous tissues.
2. Increased consumption of water.
3. Increased elimination of urea.
4. Increased rapidity of the circulation.
5. Præternatural heat.

What we have to do is to apply the above view of the nature and mode of action of contagia to the explanation of each of these phenomena.

WASTING OF THE NITROGENOUS TISSUES.

All the tissues, nitrogenous and non-nitrogenous, waste during fever. In spite of all that is done to support him, the fever patient rapidly emaciates, and wastes almost visibly before us. By two weeks of fever a strong, robust, muscular man may be so reduced as to be unable to sit up in bed, or even to turn round in it. He may have administered to him during that time a quantity of milk and beef-tea which, were he in health, would tend to make him fatter and to increase his bulk. But the fever process which is consuming him more than counterbalances our efforts to keep him up. Under it he rapidly wastes. What is this process? and how is such wasting brought about? The one cause on which we must fall back for an explanation of this and of all the other phenomena of the form of fever with which we are now dealing, is the poison which gives rise to the disease. This poison is an organism which is largely reproduced in the system during the course of the malady to which it gives rise, and which in its growth necessarily consumes a large quantity of nitrogen. The only source whence it can get this is one or other of the nitrogenous elements of the body. There exists in the system no spare store of nitrogenous material, but only what suffices for the wants of the system itself. The nitrogen requisite for the growth and propagation of the contagium must, therefore, be taken from this source, and must represent a loss to the tissues, which is directly as the extent to which the contagium is reproduced. This consumption of nitrogen by the contagium is one of the main causes of the wasting of the nitrogenous tissues which takes place in the course of the specific fevers.

But nitrogen exists in various forms and combinations, liquid and solid, in the body; and we have to consider at what point or points in its changing course through the system it is most likely to be laid hold of by the contagium.

Voit has distinguished between the fixed or organ albumen which enters into the composition of the solid tissues,

and changes slowly, and the circulating or store albumen which is contained in the blood and fluids of organs, and very readily undergoes change. But a still further distinction must be made. The circulating albumen must consist of two parts—a *constructive* and a *retrogressive*: the former derived from the assimilated ingesta, and destined for the nutrition and building up of the tissues; the latter derived from the retrograde metamorphosis of these tissues, and destined for excretion. The former is converted into solid nitrogenous tissue; the latter is converted into urea in the urea-forming glands, and as such is eliminated by the kidneys. Nitrogen thus exists in the system in four different forms—as constructive store albumen, as solid nitrogenous tissue, as retrogressive store albumen, and as urea. From which of these is the contagium most likely to take its nitrogen? Two things are likely to determine this point: first, the facility with which the nitrogen is yielded up by each of these compounds; and secondly, the special fitness of each for the purpose for which it is wanted by the contagium. The most stable of the nitrogenous compounds, and that which would least readily yield up its nitrogen, is the fixed or organ albumen; that is, therefore, the source whence the contagium is least likely to obtain its nitrogen. The increased wasting of these tissues would, on the first glance, point them out as its probable source; but such a result would equally follow the appropriation by the contagium of the nitrogen destined for their nutrition and repair.

Next in stability is the urea; next to the organ albumen it is, therefore, the least likely source from which the contagium should get its nitrogen. But there are more cogent reasons for rejecting it. First, the consumption of the nitrogen of the urea would not lead to wasting of the nitrogenous tissues—would not, indeed, have any effect on these tissues; for nitrogen does not enter into the combination which results in the formation of urea till it has served all the purposes for which it was taken into the system, and is about to be eliminated. Second, the consumption by the contagium of the nitrogen of the urea

would necessarily lead to greatly diminished excretion of that substance by the kidneys; but during the specific fevers there is increased elimination of urea. These reasons make it certain that the urea is not the source whence the contagium derives its nitrogen.

The only other available source is the store albumen. This consists of two parts—a constructive and a retrogressive. From one or both of these the nitrogen of the contagium must be derived. So far as the readiness with which their nitrogen is yielded up is concerned, the two are pretty much on a par; each is a transition compound, and has for one of its leading characteristics a readiness to undergo change and to part with its nitrogen, the one yielding it up to the albuminous tissues, the other parting with it in the gland cells which form it into urea. Any advantage which does exist is on the side of the constructive store albumen; for while this is ever undergoing change, and constantly giving up its nitrogen to the albuminous tissues in all parts of the body, the retrogressive yields up its nitrogen only in the urea-forming glands. Now, there is no reason to suppose that the growth of the contagium takes place only in these glands, or that it gets its nitrogen in them only. On the contrary, there is good reason to believe that the contagium appropriates nitrogen all over the body, and in all its tissues. But there are more cogent reasons for rejecting the claims of the retrogressive store albumen—the same reasons, indeed, which led us to reject those of the urea. The nitrogen does not go to form retrogressive albumen till it has served all the purposes of the tissues; it is no longer required by them—is, indeed, rejected by them—and assumes this form only that it may be conveyed to the glands, in which it is changed into urea for the purposes of elimination. The retrogressive store albumen is as essentially an excretory compound as is urea. The consumption of its nitrogen by the contagium, therefore, could not cause wasting of the nitrogenous tissues; it would lead only to decreased formation of urea. But all this is exactly the reverse of what takes place: the tissues do waste, and there is increased formation of urea. The

retrogressive store albumen is evidently not the source whence the contagium derives its nitrogen.

The only remaining source is the constructive store albumen; and a little consideration serves to show that it is also the one whence the contagium would by preference naturally take its nitrogen. The constructive store albumen is the source whence is derived the nitrogen destined for the building up of the nitrogenous tissues; it is only in it that they get nitrogen in the form suitable for their repair. Now, it needs no argument to show that the process by which the protoplasm of the contagium is formed bears a much closer analogy to that by which the protoplasm of the albuminous tissues is built up than it does to any other action which goes on in the system. Each is a constructive step, and essentially consists in the appropriation by living protoplasm of the elements requisite for its growth. The particular nitrogenous compound which serves to build up the protoplasm of the tissues is likely also to be the one which would best serve to build up that of the contagium. Every reason and argument thus lead to the conclusion that the source whence the contagium derives the nitrogen requisite for its growth is the constructive store albumen. A necessary result of the reproduction of the contagium in the system during the course of the specific fevers, is thus the consumption by it of the nitrogen of the constructive store albumen. This represents a direct loss of nitrogen to the nitrogenous tissues, and such loss is one of the primary causes of that rapid wasting of these tissues which forms one of the characteristic features of the specific fevers.

INCREASED CONSUMPTION OF WATER.

But though a primary, it is not the sole agency in producing this loss of bulk. All living and active protoplasm consists mainly of water. Of one hundred parts of human flesh, seventy-four consist of water. A proper supply of water is, therefore, as requisite to the nutrition of the tissues and to the renewal of their protoplasm as is a due supply of nitrogen. But water enters as largely—probably

even more largely—into the composition of the protoplasm of the contagium, and is therefore consumed by it during its growth. The growth of the contagium in the tissues means, therefore, a large consumption of the water as well as of the nitrogen destined for their repair; and this appropriation by the contagium of the water destined for them is probably as potent a factor in the production of that loss of bulk which we are now considering, as is the consumption by the same agency of the nitrogen of the constructive store albumen. Certain it is that this double loss to the tissues—the loss of water and the loss of nitrogen which must result from the growth of the contagium in the system—affords a reasonable and adequate explanation of the rapid wasting of the tissues which characterises the course of the specific fevers. This consumption of water by the contagium serves also to explain some of the other characteristic and essential phenomena of fever.

Of the subjective phenomena of the febrile state none is more prominent than thirst. To allay this there is consumed a much larger than usual quantity of water. So great is the demand for water that each draught has but a transient and temporary effect in allaying the thirst which is consuming the sufferer. Very soon another is called for, and another, and another; and the demand continues so long as the fever lasts. In this way the quantity of water consumed during an attack of fever far exceeds the ordinary requirements of the system. While this large quantity of water is being consumed, less than the normal amount is being eliminated; and hence the phenomenon with which we are now dealing is usually referred to as excessive *retention* of water. It is obvious, however, that the enormous quantity of water consumed during a febrile attack cannot be retained as water; it is equally certain that it is not eliminated, for all the while the ordinary channels of water elimination are less than usually active; the skin is dry and unperspiring, the bowels are constipated, and the urine scanty. If neither retained in the system as water, nor eliminated, it must somehow be used up in it. Parkes suggested that during the metamorphosis of the albuminous

tissues there may be formed a gelatinous compound intermediate between them and urea, and possessing in virtue of its gelatinous nature a great attraction for water. It is difficult to see how such an agency could produce such a result, or how any retrograde compound could attract water more powerfully than the tissues, which so urgently require it. But granting that it could, there are still insuperable obstacles in the way of our accepting this explanation. In the first place, why should such a compound be formed in such excessive quantity? In the second place, if the disintegrative changes of the nitrogenous tissues thus stop short of the formation of urea, how comes increased elimination of urea to be a characteristic of the vast majority of the cases in which this excessive retention of water occurs? No; the thirst of fever is an expression of a real want of water in the system; it is a cry for more; and the coincident occurrence of increased consumption and decreased elimination is distinct evidence that the water which is drunk is somehow used up in the system. But the normal ingredients and tissues of the body require no such large supply, and are incapable of utilising it. The only abnormal agency is the contagium; and this, we know, necessarily consumes a large quantity of water during its growth and reproduction. In this consumption of water by the contagium we have the explanation of the increased demand for water, and of some of the usual symptoms of fever. The thirst, the loss of appetite, the dry skin, and the scanty urine result from the consumption by the contagium of the water which is requisite to enable the stomach, the skin, the kidneys, and all the other organs to perform their functions aright; and so this phenomenon, the direct and necessary result of the propagation of the contagium, becomes the immediate cause of many of the ordinary minor phenomena of an attack of fever, as well as of some of the leading and essential ones.

Though the consumption by the contagium of the nitrogen and water destined for the nutrition and repair of the tissues is the chief, it is not the sole, agency in producing

the tissue waste characteristic of fever. A probable adjuvant cause is that 'morbid general increase of tissue metabolism' which has been regarded by the advocates of the combustion theory as not only the essence of the febrile state, but as the cause of the wasting of the febrile body. Though that wasting is, as we have just seen, mainly due to other causes, this one is not altogether void of share in its production. What we have to do is to consider how it is brought about. The evidence of its existence is not so much increased tissue waste—for that is otherwise accounted for—as increased elimination of urea, which must result from increased tissue disintegration. To this phenomenon we must therefore for a moment direct attention.

INCREASED ELIMINATION OF UREA.

Urea is formed in the urea-forming glands from the retrogressive store albumen. If the propagation of the contagium in the system is competent to cause an increased flow of retrogressive store albumen through these glands, it is competent to cause increased formation of urea. Of its competence to do this there can be little doubt. Tissue metabolism consists of two distinct processes—the taking up of new material and the giving off of old. Both actions take place in and around the capillaries, and are contemporaneous, so that it is impossible to say either that the old nitrogen of the organ albumen is deposed by the fresh nitrogen of the constructive, or that the constructive steps in to fill up a gap created by the passage backwards into the circulation of the used-up nitrogen of the organ albumen. The two actions are simultaneous—neither actually preceding the other any more than in osmosis the passage of one liquid through a membrane precedes the passage of another which exists on the other side. While this simultaneous double action is going on, the contagium particles step in and convert into their own protoplasm so much as they require of the nitrogen of the constructive albumen. The moment at which they lay hold of it is that at which it is about to be appropriated by the tissues—the moment,

that is, at which it is in the transition state which it must assume in passing from the condition of constructive to that of organ albumen. The protoplasm of the tissues and of the contagium is formed at the same time, in the same place, and from the same material; and so close is the struggle between the two for the possession of the nitrogen of the constructive store albumen that the contagium seizes upon it at the very moment at which it is about to be incorporated with the tissues, and consequently not before some of the nitrogen of the used-up organ albumen, which it was on the point of replacing, has passed back into the circulation as retrogressive store albumen. The moment at which the constructive albumen is undergoing the change which normally results in the formation of organ albumen, is that at which its nitrogen is taken up by the contagium. The simultaneous action by which the organ albumen is converted into retrogressive is equally far advanced; the contagium steps in to deprive the tissues of much of what they require and *are in the act of appropriating* for the formation of organ albumen. No such agency intervenes to prevent the completion of the contemporaneous and equally far advanced action which results in the formation of retrogressive albumen; that action, therefore, continues as usual; and thus is brought about the physiological anomaly that a diminished consumption of nitrogen by the tissues is accompanied by an increased elimination of nitrogen by the kidneys.

Another and essential phenomenon of fever intervenes to aid this result. Tissue metabolism depends, among other things, on the circulation through the tissues of a due supply of blood. The more active the circulation the more active, *cæteris paribus*, will be the tissue changes. In health the heart beats at the rate of about seventy a minute, and at each beat sends onwards about the same quantity of blood, so that in twenty-four hours the heart has sent the fill of its left ventricle through the body 100,800 times. In fever there is increased rapidity of the heart's action and of the circulation through the tissues. Supposing it to beat 120 times per minute, the fill of its

left ventricle would be sent through the circulation 172,800 times in twenty-four hours. As there is no diminution, but rather an increase, in the amount of retrogressive albumen in the blood, it is evident that one result of the increased rapidity of its circulation must be the conveyance in a given time to the urea-forming glands of a more than usual quantity of the material from which urea is formed, and consequent increased formation of urea; and thus is brought about the phenomenon which we are now considering, increased elimination of urea.

The view here advocated as to the mode of action of the contagium, and as to the mode of production of the wasting of the tissues and of the increased elimination of urea, serves to explain why it is that in fever the salts of soda are retained in the system, while the salts of potass are eliminated in increased quantity. The salts of soda exist chiefly in the liquor sanguinis; they are retained because the contagium in consuming the essential ingredients of the liquor sanguinis (nitrogen and water) necessarily takes up also the soda salts which exist in it. The salts of potash exist chiefly in the tissues. The increased disintegration of these to which the contagium gives rise is followed by increased elimination of their constituent elements, hence it is that increased elimination of urea in fever is accompanied by increased elimination of potass salts.

PRÆTERNATURAL HEAT.

Another and necessary result of increased tissue metabolism is increased production of heat, the phenomenon whose causation we are supposed to be specially investigating when considering the theory of fever. This increased body heat is only one of a group of phenomena, each of which is the direct or indirect result of the propagation of the contagium in the tissues. The *direct* action of the contagium consists in the consumption by it of the nitrogen and water of the constructive store albumen. The *indirect* results of this (and, therefore, the indirect effects of the propagation of the contagium) are :—

1. Impoverishment and consequent wasting of the nitrogenous tissues.

2. Increased demand for water, with its attendant thirst, dry skin, scanty urine, and constipated bowels.

3. Increased tissue metabolism, with its attendant increased rapidity of the circulation, increased frequency of pulse, increased formation of urea and carbonic acid, and increased production of heat. Thus we find that the phenomena which must necessarily result from the propagation of an organism in the tissues are exactly those which are found to characterise the febrile state. Thus is explained the mode of action of the poisons of the specific fevers: and thus is exemplified the metabolic theory of fever.

From what has been said, it is apparent that the view which regards the action of the contagium as being on the blood and tissues, has much more to commend it than that which would attribute it to an action on the nervous centres.

That such increased activity of tissue metabolism as that to which, on this view, the contagium gives rise, cannot take place without disturbance of the centres which preside over that metabolism is undoubted; and to some extent that centre must participate in the general derangement: but such disturbance of the nervous centres is secondary to, and consequent on, disturbance originating in the blood and tissues, and cannot for one moment be regarded as primary, or as in any way initiating the febrile phenomena. To call such fever neurotic would be most inaccurate. After the febrile process is fairly under way, disturbance of nerve centres may and often does to some extent influence or modify its course: for it is evident that the continuance for any length of time of excessive formation of heat may lead to fatigue of the heat-inhibiting function, and to some amount of fever from this cause.

So, too, a local complication, even the specific local lesions of the eruptive fevers, may give rise to some degree of neurotic pyrexia—such pyrexia as would accompany a like inflammation occurring independently of the general fever.

This is a contingency which has to be borne in mind in treatment, and will be again referred to when the anti-pyretic action of cold is under consideration.

To another occasional incident in the specific fevers a reference must here be made.

DECREASED ELIMINATION OF UREA.

A necessary result of increased metabolism is increased formation of urea. Increased formation naturally leads to increased elimination. But every now and then cases occur in which the urea elimination is below the normal standard. How is this? How can an agency which, in one case, gives rise to increased elimination of urea, in another give rise to exactly the opposite result?

The diminished excretion of urea, which is noted in some cases of fever, was attributed by Dr. Parkes, not to diminished formation of excretory products, but to the retention of these products in the blood: and he suggested such retention as a cause of many of the phenomena which occur in the course of a febrile attack; and especially of the local inflammatory complications which are occasionally found in cases in which there is decreased elimination of excreta. The copious discharge of products so retained he looked upon as explanatory of the phenomena observed at the crisis. In other words, the decreased elimination of urea was attributed to defective action of the kidneys.

The condition to be considered is one in which urea formation is in excess of urea elimination. That the structurally sound kidney is capable of eliminating a much larger quantity of urea than is habitually excreted in health, is proved by the fact that in fever and other ailments the normal quantity is often greatly exceeded; and by the additional fact, that when one kidney is by any means lost, the remaining one does as much work as was previously done by two. That there is a limit to the excreting power of the kidneys there can be no doubt: it is, therefore, possible that there might be produced more urea than the kidneys are competent to eliminate, and that uræmia might thus result,

solely from excessive formation of urea—the amount eliminated, though above the normal standard, being still inadequate to counterbalance the excessive formation. This, however, would not constitute defective action of the kidneys, and would not give rise to the phenomenon which we are now considering, decreased elimination of urea.

What we have to deal with is a condition in which there is decreased elimination of urea without evidence of decreased formation; and what we have to consider is, whether or not this decreased elimination results from defective action of the kidneys.

Cases of fever accompanied by decreased elimination of urea may be divided into two classes—those in which the kidneys were diseased prior to the occurrence of the febrile attack, and those in which they were healthy at the time of its onset.

That a febrile attack, occurring in one who is the subject of renal disease, should be more or less modified by the previously existing ailment, and that the symptoms of the kidney disease should, in their turn, be intensified by the grafting on to them of those referable to the febrile attack, is no more than one would expect. We know that, without the prior existence of any renal complication, bad cases of fever are apt to present features which bear a very close resemblance to those presented by advanced cases of renal disease. It is not, therefore, to be wondered at that fever occurring in one who is the subject of renal disease, should present, in an unusually marked manner, those symptoms which are apt to occur in each of these ailments from which he is suffering; and which, in both, have been attributed to the same cause, defective elimination of excretory products. The existence of renal disease in those suffering from fever only increases the risk of defective elimination of excretory products, and of the occurrence of so-called uræmic symptoms. We need not, therefore, enter into a detailed analysis of such cases, but may at once proceed to the consideration of those in which there is decreased elimination of urea, but in which the kidneys are healthy at the onset of the febrile attack;

premising only, that everything said regarding the mode of production of the renal symptoms in them, is doubly applicable to those in which there was previous disease of the kidneys.

Finding the evidence of defective renal action, and the occurrence of serious nervous symptoms, constantly co-exist, the nervous symptoms have naturally been looked upon as the consequence of retention of excreta: the head symptoms are supposed to be of uræmic origin, and (what concerns us at present) the decreased elimination of urea, and its retention in the blood, are attributed to morbid change in, and defective action of, the kidneys.

But how are the morbid changes in the kidneys produced? We know that in such cases the kidneys are perfectly healthy at the commencement of the febrile attack; that in those which recover the urinary secretion again, as a rule, becomes normal; and that, in those which prove fatal, the morbid appearances presented by the kidneys are recent. We know, in short, that the renal disorder is secondary to the fever, and results, either directly or indirectly, from the action of the fever poison. That it is not due to any *direct* action on the kidneys of the poison which gives rise to the febrile symptoms, is rendered certain by the fact that such disorder occurs in only a small number of the total cases of fever: that it is due to some *indirect* action of the poison, is proved by the fact that it manifests itself subsequently to the onset of the febrile state, and that, in cases which recover, it disappears after defervescence.

Again, the fact that the symptoms of renal disorder occur in only a small number of cases, shows that those in which they do occur must be in some way peculiar, and that the direct cause of the renal complication is not to be found in any *necessary* condition of the febrile state.

Let us then analyse these cases, and try to find out wherein their peculiarity consists.

The first thing to be noted regarding them is, that they are all severe—the febrile symptoms running high from an early period: even before the appearance of any renal com-

plication, there is great thirst, rapid pulse, high temperature, and specially prominent nervous symptoms. As the fever advances, the symptoms become more marked; delirium is constant, often violent, and not unfrequently, culminates in convulsions, coma, and death; at the same time the urine is scanty and high-coloured, is frequently albuminous, often contains casts of the renal tubes, with excess of renal epithelium, and at times is tinged with blood. In fatal cases, the kidneys give evidence of irritation, or even of inflammation; they are increased in size, and more or less gorged with blood: their tubes are loaded with epithelium, occasionally mingled with blood—the evidence of renal disorder being recent.

Besides the occurrence of renal disturbance, and defective elimination of urea, the chief peculiarity of the cases now under consideration is the height to which the fever runs. Cases in which the temperature is high at an early period of the attack, are those in which we are likely to have albuminuria, and bad head symptoms.[1] But it is to be particularly noted, that all the febrile symptoms are thus marked before there is evidence of renal disturbance, and that the early occurrence of a high temperature only leads us to be on the outlook for such a complication. Now, what peculiarity do these cases present, prior to the occurrence of evidence of renal disorder, and, maybe, even before there is diminished excretion of urea? And what is there in them that should lead to such a complication? Nothing apparently, beyond an unusually smart attack of fever. Well, what does this imply? It means that the various actions, the existence of which in the body the febrile state implies, are taking place in a more than usually marked manner: it means that there is a very large propagation of contagium particles, a greater than usual consumption of nitrogen and water, a greatly increased formation of retrogressive albumen, a more than ordinary increase in the rapidity of the circulation through the tissues, and an unusually large formation of urea. To one feature in these cases we would

[1] See Paper by Author on the *Thermometry of Typhus*, in *Edinburgh Medical Journal*, vol. i. 1869.

draw special and prominent attention—the greatly diminished excretion of water. *We never find diminished excretion of urea in fever, with a normal quantity of urine.* Defective excretion of water is, indeed, even more characteristic of the cases which we are now considering, than is defective elimination of urea. In their early stages, the quantity of urea eliminated may be, and generally is, in excess of the normal; but the quantity of urine is always more or less scanty. But one interpretation can be put on this: the kidneys are quite competent to perform their function; they excrete a larger than normal quantity of urea, because a larger than normal quantity is sent to them; they excrete an abnormally small quantity of water, because they cannot get more. But, let the cause which gives rise to both these conditions (the propagation of the contagium) pass a certain limit; let urea be formed, and sent to the kidneys in such large quantity, that the eliminating capacity of these glands is taxed to a greater than normal extent; and let the quantity of water placed at their disposal be at the same time so deficient, that they can get very little to excrete, and defective excretion of urea must result—not because the kidneys are affected, not because they are incompetent to excrete urea, but because the conditions requisite to its excretion are not to be had. The diminished excretion of urea, then, is due not to diminished formation of that substance, not to structural change in the substance of the kidneys, but to the absence of the quantity of water which is essential to the formation of urine, to the elimination of the urea, and to the due performance of their functions by these glands. It is thus an indirect result of the propagation of the contagium.

What must be the effect of all this on the kidneys themselves? And how are we to explain the albuminuria, and other evidence of disorder, which they so frequently present, in conjunction with the diminished excretion of urea?

The circumstances with which we have to deal are, (1) that there is a great and increasing excess of urea in the blood, and (2) that the quantity of water necessary to its elimination by the kidneys is not to be had. Now, it is

evident that this unusual quantity of urea cannot circulate, and continue to circulate, through the kidneys, with no possibility of elimination, without seriously irritating these glands. The action of urea on the nervous system is still a matter of discussion; but of its action on the kidneys there is no doubt: it is decidedly stimulant to these organs, as is manifested by its normal action on them, and by the fact that its injection into the circulation gives rise to diuresis. It is obvious that if this stimulation be excessive, irritation and even inflammation may result; it is equally obvious that this stimulation must be excessive, and that there must, therefore, be considerable renal irritation in those cases of fever in which excessive propagation of the contagium leads at once to excessive formation of urea, and increased consumption of water. The defective elimination of urea, therefore, is not secondary to the morbid changes which take place in the kidneys; but these changes, and the evidences of renal mischief which, as a consequence of them, are noted in the urine during the patient's lifetime, are the result of the uræmia, and the consequent presence in the kidneys of an excessive quantity of their natural stimulant, which, for reasons already given, they are unable to eliminate. The ultimate cause of both the uræmia and the renal symptoms, is the excessive propagation of the contagium.

The appearances presented by the kidneys bear out this view. Referring to typhus fever, Murchison says, 'If death occur before the fourteenth day the organs are usually hyperæmic and hypertrophied, while the tubes are gorged with granular epithelium and sometimes contain blood. Occasionally they present the appearances of acute nephritis, as intensely developed as in any case of scarlatina.' (Murchison, 2nd ed. p. 265.) The urine secreted by such a kidney must be albuminous, and contain tube casts, and sometimes blood. The appearances thus described by Murchison are exactly those which would be produced by the circulation through the kidneys of something which would be stimulant, or irritant, according as it existed in greater or less quantity. Is not urea the substance which, if unduly retained in the circulation, would be most likely to produce

such an action? Is it not the case that urea is unduly retained, and does circulate in undue quantity through the kidneys in cases in which the renal symptoms are marked? And is it not the case, that we do not know of the existence in the blood of any other agency capable of producing such an action on the kidneys? And, finally, is not this view of the pathology of the renal changes occurring in the course of idiopathic fever, the necessary and logical inference to be drawn from such an exposition of the facts as has been given?

When the quantity of contagium produced in the system is not too great, the amount of urea formed is not above that which the kidneys are capable of excreting. There is increased formation of urea, but there is also increased elimination. When, however, the propagation of the contagium passes a certain limit, there is produced, as a consequence of the greatly increased rapidity of the capillary blood flow, not more urea than the kidneys could excrete, if they could get the necessary quantity of water, but more than they are capable of eliminating with the small quantity of water which is at their disposal. It is thus that the uræmia is produced; and it is the continued circulation through, and presence in, the kidneys, of an excess of their normal stimulant, which gives rise to irritation, and, maybe, even to inflammation of these organs, and leads to the symptoms, and morbid appearances, presented by the urine and kidneys of many of those cases of fever in which there is defective excretion of urea. The kidney affection, therefore, is secondary to the uræmia.

A consideration of the phenomena presented by those cases of fever in which there is decreased elimination of urea, and a minute study of the circumstances which precede and lead up to this, have led us to the conclusion that this decreased elimination results not from decreased formation of that substance, but from defective excretion by the kidneys; this in its turn results, not from morbid change in these glands, and not from want of excreting power in them, but from the absence of the quantity of water which is necessary to enable them to form urine, and to eliminate

the urea which is circulating through them. This defective supply of water results from its excessive consumption by the contagium particles. The ultimate cause of the defective excretion of urea, and of all the phenomena resulting therefrom, is, therefore, excessive reproduction of contagium particles—the same agency which, occurring in a minor degree, we have seen to be also the ultimate cause of the increased elimination of urea common in fever.

The connection between the febrile state, as it presents itself in the specific fevers, and the elimination of urea may be briefly stated thus. The febrile state is always accompanied by increased formation of urea, and by increased consumption of water, the two chief ingredients of the urine. So long as the quantity of water at the disposal of the kidneys is sufficient for the purpose, there is increased elimination of urea. In severe cases, in which there is a large propagation of contagium particles, the balance is apt to be disturbed; there is, in them, a very great consumption of water, and a coincidently great increase in the amount of urea formed. The kidneys are thus placed in the position of the Israelites of old, when they were ordered to make bricks without straw; they have more than enough urea, but scarcely any water with which to form urine. If this abnormal state of affairs be not excessive, or do not continue too long, the difficulty may be tided over, with no more than an anxious and smart attack of fever, accompanied by very scanty excretion of urine, but not by any very marked renal complication. If the disturbance be excessive, however, and manifest itself at a comparatively early period of the attack, renal symptoms are inevitable; albumen appears in the urine, then casts of the renal tubes are detected, and even blood may appear; there is greater or less retention of urine, greatly diminished excretion of urea, and very prominent nervous symptoms; the patient either lapses into a state of coma, in which he dies; or makes the narrowest of escapes.

Between the mild attack in which neither the increased elimination of urea nor the decreased elimination of water is at any time marked, and the severe one in which there

is at last complete suppression of urine, there are all shades and degrees.

Such is the explanation which the germ theory offers of the essential phenomena of the febrile state as these present themselves in the specific fevers. It shows these phenomena to be, not of neurotic, but of metabolic origin. But to explain the essential phenomena of these fevers is not enough. Such explanation may, indeed, suffice for the physiologist who concerns himself only with the rise of temperature. But it will not suffice for the practical physician who studies fever as he finds it at the bedside. Other phenomena and changes, and other clinical features there are, which in his mind are as intimately associated with the action of the poisons of these fevers as those essential phenomena which we have been considering. These clinical features equally call for consideration; and no theory of fever can be regarded as satisfactory which does not afford an adequate explanation of their occurrence.

The points which specially demand attention are:—

1. The nervous symptoms.
2. Typhoid symptoms.
3. The mode of death.
4. The changes noted after death.
5. The occurrence of local lesions.
6. The different degrees of contagiousness of the specific fevers.
7. The different degrees of severity of the same form of fever.
8. The cessation of the febrile symptoms.
9. The fixed duration of the fever.
10. Immunity from second attacks.
11. Relapsing fever.
12. The treatment of fever.

THE NERVOUS SYMPTOMS OF FEVER.

These are rigors, headache, delirium, convulsions, and coma.

Rigors.—The first symptom of the onset of the stage of

invasion of fever, the first decided intimation of the presence of the contagium in the body, is the occurrence of a feeling of cold. In accordance with the humoral pathology which held sway in his time, Boerhaave ascribed the cold stage of fevers to viscidity of the blood leading to its stagnation in the minute vessels. For a long time this doctrine was maintained by his followers. Hoffman, discarding the doctrines of the humoralists, and turning to the solids, regarded the nervous system as the seat of the mischief, and attributed the phenomena of the cold stage to spasm of the extreme vessels, resulting from a pre-existing morbid state of the blood.

Cullen adopted, and gave popularity to, this doctrine; but attributed the spasm, not to the remote causes of the fever, but to the *vis medicatrix naturae*. 'It is, therefore, presumed that such a cold fit, and spasm, at the beginning of the fever, is a part of the operation of the vis medicatrix; but, at the same time, it seems to me probable that, during the whole course of fever, there is an atony subsisting in the extreme vessels, and that the relaxation of the spasm requires the restoring of the tone and action of these.' (First lines of Practice of Physic, 'Pyrexiæ.')

Rigors essentially consist in a feeling of cold: this, be it remarked, is a mere feeling, for while the patient is shivering, the temperature of the body is really above the normal standard. How is this brought about? How is the feeling of cold produced? And how can such a decided sensation be accompanied by an actual rise of temperature in the part which feels cold?

When a substance having a lower temperature than the body comes in contact with any part of its surface, caloric passes from the body to this substance, producing in the former loss of heat, and consequent sensation of cold at the point of contact. The local change which gives rise to this feeling of cold essentially consists in contraction of the minute arteries of the skin; and this, in its turn, results from stimulation of the nervous apparatus which controls the movements of these vessels, the vaso-motor system of nerves. The ultimate internal cause of the sensation of

cold, is thus abnormal excitation of that part of the vaso-motor system which excites to contraction the muscular coat of the minute arteries. Such excitation is usually due to the application of some external agent. If, however, there existed in the system any agency capable of giving rise to the same abnormal contraction of the minute arteries, it is most probable that the sensation of cold would be produced thereby, without the intervention of any external agent.

We have seen that the essential phenomena of the specific fevers are the necessary result of the propagation in the system of an organism which has wants and demands identical with those of the tissues; and which lays hold of the material essential for their nutrition at the moment at which it is about to be appropriated by them. The propagation of such an organism in the tissues necessarily leads to increased demand for blood in them, and yet to coincident diminution of the material necessary for their nutrition. There is an increased demand for blood, because the contagium particles require the same materials as the tissues; there is diminution of nutrient material, because the contagium particles appropriate what is destined for the tissues. There result from this, quickening of the circulation through the capillaries, increased retrograde tissue change, and yet diminished formation of tissue. Such derangement of the circulation, of the whole process of nutrition, and of the normal tissue changes, could not fail to make itself felt in that part of the nervous system which presides over the muscular elements of the minute arteries whose duty it is to regulate the supply of blood to the tissues. These vessels, by increase or diminution of whose calibre the blood supply to a given part is increased or diminished, are accordingly excited to increased contraction, with the object of checking the abnormal haste and waste, and of bringing matters to a more natural state. Contraction of the minute arteries thus becomes the first step in the production of the stage of invasion, and symptoms referable thereto, the first subjective phenomena of fever. As the cause which gives rise to this (the propagation of the contagium) is confined to no particular part of the body,

but acts with equal force wherever the blood penetrates, it follows that the resulting contraction of the minute arteries is also general. It is this general contraction of the minute arteries of the skin which gives rise to the general feeling of cold which ushers in the febrile attack; and it is its general diffusion over the surface of the body which imparts to this sensation the features by which it is distinguished from a similar sensation produced by external agencies. In the latter case the feeling of cold is most felt at the point of contact with the cold body; in the former it is at no point predominant. Ask a man suffering from a rigor where he feels cold, and his answer is 'all over;' he cannot point to any one part in which the sensation predominates, because the contracted state of the vessels which gives rise to the sensation exists in an equal degree all over the body.

It is thus that the occurrence of the shiverings which mark the onset of the stage of invasion of fever are to be explained. They are due to a general contraction of the minute arteries of the skin, resulting from the effort which is made by the vaso-motor centres to control and stay the too rapid flow of blood through the capillaries, caused by the propagation of the contagium.

The action of the contagium commences as soon as it begins to be propagated. Such being the case, it follows that the quantity of contagium reproduced up to the time of the occurrence of the rigors (*i.e.* during the period of incubation), must have some effect in raising the temperature; so that when the rigor occurs the feeling of cold is accompanied by an actual increase of body heat. Not indeed till the propagation of the contagium particles has gone so far as to cause derangement of the nutrition of the tissues, increased rapidity of the capillary blood flow, increased tissue change, and *increased production of heat*, does it make its presence felt in such a way as to cause disturbance of vaso-motor centres, and consequent contraction of the minute arteries.

Headache.—The contraction of the minute arteries is, of course, not confined to the vessels of the skin, but affects

those of the whole body. We accordingly find that the feeling of cold, which ushers in the febrile attack, is accompanied by other symptoms referable to anæmia of this or that organ.

The headache, which is the most constant of these symptoms, is usually attributed either to the action of the morbid poison on the brain, or to the circulation through it of impure blood. That it does not result from either of these agencies is sufficiently attested by the fact that the headache is severe only during the first few days of the febrile attack, and diminishes in intensity, or even altogether disappears, at a later stage, when the morbid poison is more abundant, and the impurity of the blood more marked. The true cause of the headache is to be found in anæmia of the brain resulting from contraction of the minute cerebral arteries, produced in the same way, and by the same cause, as the contraction of the same vessels in the skin and other organs of the body. This contraction of the minute arteries is due, not to an effort to exclude a morbid agency, but to an effort to bring under control the excessive action which is going on in the tissues, and to moderate the too rapid flow through the capillaries, which the propagation of the contagium induces.

The contraction of the vessels being general, it follows that the symptoms resulting therefrom are also general, and in no organ necessarily predominant. Those referable to the skin and nervous system are most prominent, because these organs are more sensitive and impressionable than the organs generally, and consequently give subjective evidence of derangement in a more decided manner. But the other organs also suffer from the general contraction of the minute arteries. To anæmia of the muscles thus produced are to be ascribed the muscular tremors which so often accompany true rigors. To a similarly induced contraction of the minute arteries of other parts of the body, are due other of the early symptoms of a febrile attack. Anæmia of the spinal cord thus induced causes aching in the back and limbs: contraction of the minute vessels of the heart and lungs gives rise to the feeble pulse

and oppressed breathing so commonly noted: defective supply of blood to the digestive organs, due to contraction of their minute arteries, gives rise to loss of appetite; and the general result of this generally defective supply of blood, is that undefined feeling of misery and general *malaise*, which is one of the earliest indications of commencing illness.

Anæmia of the brain we know to be a potent cause of nervous disturbance. Even violent convulsions may result from sudden and copious loss of blood; and it is a recognised fact in pathology, that the direct cause of an epileptic seizure is frequently contraction of the minute cerebral arteries. The analogy between the condition which induces such a seizure, and that which gives rise to the headache of the early days of a febrile attack, is evidenced by the fact, that it happens occasionally in the adult, and frequently in childhood (when the nervous system is particularly active and susceptible), that the headache of the stage of invasion is replaced by well-marked convulsions. The convulsions, in such cases, are due to the same cause which gives rise to the convulsions of epilepsy, and to the headache which usually ushers in the febrile attack, cerebral anæmia resulting from contraction of the minute arteries of the brain.

After continuing for a time which varies from a few hours to as many days, the evidence of arterial contraction passes off, and a corresponding change is noted in the symptoms. The sensation of cold is replaced by a feeling of heat; depression and languor give way to restlessness; and the headache is usually replaced by other symptoms referable to deranged action of the sensorium—wandering and delirium.

Delirium is usually attributed to blood-poisoning, to the action on the nervous centres of retained excreta. That blood-poisoning is a possible cause of delirium there can be no doubt: the action of many toxic agents, and the occurrence of this symptom in cases of Bright's disease, in which there is defective elimination of excretory products, sufficiently attest this.

There are good reasons, however, for not attributing the

delirium of fever to this cause alone. In the first place, this symptom is frequently found in cases in which there is being eliminated more than the normal quantity of urea, and in which there is no reason to suppose that excretory products are retained in the blood. In the second place, retention of urinary excreta is not necessarily followed by delirium. And, in the third place, there is at work another agency which affords of the change in the nervous symptoms of fever an explanation which is more satisfactory, and is, at the same time, more in accordance with what we have seen to be the mode of production of the other symptoms which precede the occurrence of delirium.

The headache which precedes it, we have seen, results from cerebral anæmia due, directly to contraction of the minute cerebral arteries, indirectly to the propagation of the contagium. But when headache is merged in delirium, the propagation of the contagium does not cease; on the contrary, it continues to be formed in increased quantity, and there is a corresponding and consequent increase in the capillary blood flow and in the tissue changes. Thus we have, in an exaggerated degree, the same changes which led to contraction of the minute arteries and the consequent rigors and headache, at the onset of the stage of invasion.

What, then, is the state of these vessels, now that the feeling of cold is replaced by a sensation of heat, and the headache gives place to delirium? Does the contraction cease, while the cause which gave rise to it is in full operation? That the contraction does give way, and that the flow of blood through the capillaries is greatly increased and accelerated, after the first few days of the stage of invasion have passed, there can be no doubt; the essential phenomena of fever, subjective and objective, afford sufficient evidence of this. The patient, instead of feeling cold, complains of heat; instead of being pale and pinched in appearance, his face is hot and flushed; the eyes are suffused; and the previously chilled aspect of the surface of his body is replaced by as general a glow of heat; a condition which points to relaxation of, and increased flow of

blood through, the minute vessels, as surely as the previously chilled aspect indicated the opposite state.

How is this change in the condition of the minute arteries brought about? It might be due to simple exhaustion and consequent relaxation of the contracted fibres. Such a cause is evidently not powerless to produce (within certain limits) such a result. It is equally evident, however, that it cannot be the chief agency; for it is difficult to see how mere exhaustion could lead to the long-continued relaxation by which, in the present case, the contraction is followed. Relaxation resulting from such a cause would not be so continuous as that which obtains in fever, but would again give place to contraction as soon as the exhausted fibres had recovered their tone.

It is evident that there must be some other and more potent agency at work. Such an agency we find in the great and increasing demand for blood in the brain and other tissues, the result of the propagation in them of the contagium particles.

When considering the cause of the rapid emaciation, and of the quickened circulation of fever, we saw that the demand for blood to which the propagation of the contagium in the tissues gives rise, is practically indistinguishable from that which would result from a like increase in the natural wants of the tissues. During the period of incubation the propagation of the contagium is not sufficient to cause disturbance. By-and-by, as its propagation increases, the hastening of the blood flow, and consequent increased tissue waste, produce on the vaso-motor centres an impression which leads to contraction of the minute arteries (the regulators of the blood supply) and a consequent feeling of cold. This contraction, however, is powerless to stay the course of events. The contagium rapidly increases and grows in the minute structure of the tissues; and by consuming the materials required for their nutrition, causes a greatly increased demand for blood in them, a demand which continues to increase with the growth of the contagium. But contraction of the minute arteries is incompatible with the satisfaction of such a demand. We

accordingly find that, as the growth of the contagium increases, these vessels, still in the due performance of their normal function, relax, and permit of the passage to the tissues of what they so urgently call for. As the urgency of this call increases, and the circulation through the tissues becomes more rapid (as both must do as the contagium is more abundantly propagated) these vessels pass from a state of abnormal contraction to one of abnormal relaxation. We accordingly find that, after a few days, the chilliness and headache pass off, and are replaced, the one by a sensation of increased heat, the other by wandering and delirium. The time at which this change in the symptoms takes place marks the period at which the abnormal contraction of the minute arteries gives rise to relaxation.

Is it, then, the increased flow of blood through the cerebral tissue which gives rise to the change in the nervous symptoms? By no means. The change which takes place is due neither to relaxation of the minute arteries, nor to any direct result of the altered condition of these vessels, but is to be ascribed to the cause which produces this relaxation. This cause is the excessive demand for blood consequent on the greatly increased growth of the contagium in the tissues. The change in the nervous symptoms results from the consumption of the essential constituents of the blood (nitrogen and water) by the contagium, and consequent malnutrition of the brain tissue. Increased propagation of the contagium is thus the cause both of the arterial relaxation and of the coincident change in the nervous symptoms. In the production of this change there are various agencies at work, all referable to that one cause. There is increased consumption of nitrogen and water; there is a consequent hastening of the blood flow; there is diminished nutrition of brain tissue; and yet coincident increase in its retrograde changes. There is, in short, going on in the brain exactly the same action which in the muscles leads to the wasting characteristic of fever. We thus have at one and the same time, defective nutrition and increased metamorphosis of cere-

bral tissue. Such a state of matters must, in so delicate an organ as the brain, give rise to marked derangement of function. Functional disturbance of the brain generally declares itself by wandering and delirium. We accordingly find, that delirium is of frequent occurrence at that stage of a febrile attack at which the nutrition of the brain is seriously interfered with in the manner indicated. In mild cases, in which comparatively little contagium is formed, the nutrition of the brain is not seriously affected, and there may be no more than a tendency to wander at night: in severe cases, in which there is a large reproduction of the contagium, greatly impaired nutrition, and increased cerebral waste, the delirium is constant, and often violent.

Convulsions.—These occur at two different stages of idiopathic fever, (1) at its commencement, and (2) at its height.

(1). The convulsions of the stage of invasion are almost peculiar to childhood, and generally pass off without bad effects. In childhood the nervous system is particularly delicate and susceptible, and consequently suffers more severely than that of the adult from any disturbing cause. When considering the cause of the rigors and headache which usually usher in the stage of invasion, we found that these were due to anæmia, resulting from contraction of the minute arteries of the skin and brain. The contraction of the cerebral arteries which in the adult gives rise only to headache may, in the highly susceptible nervous system of the child, cause well-marked convulsions, which, however alarming in appearance, are rarely a source of danger; they generally pass off without bad effect so soon as the disease is fully developed, and so soon as the minute arteries pass from a state of contraction to one of relaxation. The convulsions of the stage of invasion, instead of being (as is usually supposed) the direct result of the action on the brain of a morbid poison, are really due to cerebral anæmia, similar in character to that which, in the adult, gives rise only to headache, lassitude, and *malaise*.

(2). The convulsions of the fully developed disease are much more serious, and form one of the gravest complica-

tions of idiopathic fever. They are generally regarded as of uræmic origin, as being due to the action on the nervous centres of retained excretory products, chiefly urea. The reasons for this belief are, (*a*) that, in cases with such marked head symptoms, there is defective elimination of urea; (*b*) that in such cases the blood and other fluids have frequently been found to contain an excess of that substance; (*c*) that the urine in such cases is not only scanty, but is nearly always albuminous; (*d*) that the kidneys of those who die of convulsions generally present morbid appearances; and (*e*) that there is no other cause competent to produce such a result.

Of the fact that there is almost, if not quite, invariably, retention of excretory products (chiefly urea) in cases in which convulsions occur, there can be no doubt. The question which we have to consider is the connection which exists between this state of the blood and the nervous symptoms.

As already stated, the view generally held is that the retained excreta exercise a toxic action on the nervous centres, and that the nervous symptoms are due to such action. The reasons for this belief have just been given.

But there are difficulties in the way of accepting this view of the matter. In the first place, it is to be noted that urea may exist in excess in the blood, and may be injected into the circulation, without producing disturbance of the nervous centres. Impressed with the strength of this objection, Frerichs[1] advanced the hypothesis that the real toxic agent is carbonate of ammonia. Rosenstein[2] supports this view. Oppler,[3] on the other hand, believes that the real toxic agent is neither urea nor carbonate of ammonia, but simply increased metamorphosis of the central organs of the nervous system. This view has much to commend it, but does not probably express the whole truth.

In its ultimate bearing, the opinion of Frerichs differs very little from that which was generally held before it was advanced; and it is open to the same objections. The

[1] *Die Brightsche Nierenkrankheit*, 1851.
[2] Virchow's *Arch.* 1873, Bd. lvi. Heft 3.
[3] *Ibid.* 1861, Bd. xxi. Heft 3.

pathological question which presents itself for our consideration, is not whether excess of this or that product of tissue metamorphosis may give rise to serious nervous symptoms; but whether *any* product of such metamorphosis is the cause of the disturbance with which we have to deal.

We believe that the view generally held (that the nervous symptoms are due to the toxic action on the nervous centres of some direct or indirect product of tissue metamorphosis) is an erroneous one. The reasons for this belief are (1) That the products which are supposed to give rise to this toxic action may accumulate in, and be injected into, the circulation without causing disturbance of the nervous centres: (2) that nervous symptoms are not peculiar to cases in which excreta are retained, but are more or less observed in all cases of fever, and therefore, probably result from some cause which operates in all cases: (3) that there is in operation, during the course of the eruptive fevers, an agency whose competence to produce serious disturbance of the nervous centres, is undoubted.

Cases in which convulsions occur are, *cæteris paribus*, more severe than those in which there is only delirium. Their greater severity is due to a larger propagation of contagium particles. It is evident, therefore, that the symptoms which they present may be due to an exaggerated degree of the same cause which gives rise to the less prominent symptoms of milder cases; that, in short, the disturbance in the cerebral circulation and nutrition which, in an ordinary case, suffices only to cause delirium, may, in a severe one, be sufficiently great to induce convulsions.

But this is not the complete history of the pathology of convulsions. We have already seen that the same cause to which we now ascribe an important part in the production of serious cerebral symptoms, also produces serious interference with the eliminating action of the kidneys; so that, coïncidently with increased formation, there is decreased elimination, and consequent retention, of excretory products.

Now what is the effect of all this? and what part does such retention play in the production of those alarming

nervous symptoms in connection with which it is chiefly noted? To assert that the retention in the blood of excretory products does not cause disturbance would be to run counter to all clinical experience and observation. We believe that such products do materially aid in the production of the nervous symptoms noted in connection with their retention in the blood; but that the part which they play is not primary, but secondary to, and adjuvant of, that played by the agency to which we have just ascribed the delirium. In other words, retained excreta do not produce convulsions in fever by a direct toxic action on the nervous centres: they merely aid in the production of such symptoms by increasing the already existing malnutrition of these centres. This they do chiefly by interfering with the retrogressive, and so indirectly with the constructive changes.

These retrogressive changes consist in the separation from the tissues of their worn-out material. Now, if the blood be unduly loaded with these excretory products, it is evident that the interchange of material which takes place between the tissues and the blood (and which constitutes the process of nutrition) will be, to some extent, hindered; the presence in the blood of an excess of the products of tissue metamorphosis being, by the ordinary laws of diffusion, a bar to their continued free passage back into it, and, consequently, a bar to the due nutrition of the tissues.

To put it otherwise. Defective elimination by the kidneys leads to retention of excretory products: retention of excretory products leads to defective retrograde tissue change: the tissues, not throwing off their old and worn-out material, are unable to take up new: the whole process of nutrition is thus deranged from behind forwards; and that, too, at a time when, by the direct action of the contagium on the liquor sanguinis, it is being seriously disturbed from before backwards. The candle, in short, is being burnt at both ends, and with the usual result of such an operation. It is to this twofold interference with the nutrition of the brain tissue that we have to look for an explanation of those alarming nervous symptoms, which are noted in cases in which the febrile symptoms run high, and

in which there is marked diminution in the quantity of excreta eliminated.

The way in which retained excreta act in the production of these symptoms is readily explained, and illustrated, by what occurs when an animal is placed in an atmosphere of carbonic acid. An animal placed in such an atmosphere speedily dies asphyxiated; but it is not killed by any direct poisonous action of that atmosphere: it dies because, by the ordinary laws of diffusion, carbonic acid cannot be eliminated from the system in such an atmosphere. Retention of excretory products in the blood acts on the tissue respiration in the same way as an atmosphere of carbonic acid acts on the pulmonary. The excreta which are in the blood exercise no direct toxic action on any tissue; they simply put a stop to the tissue respiration: they are as effectual a bar to the passage back into the circulation of the products of tissue metamorphosis, as an atmosphere of carbonic acid is to the passage outwards of that gas from the system. The more they accumulate in the circulation, the greater will be the interference with the tissue changes, and the more marked the symptoms produced. All the symptoms thus induced must be attributed to interference with the process of nutrition. The organ which suffers most from any such interference is the brain. It is so delicate and so active an organ, and requires so large a supply of blood, that any general interference with the process of nutrition is almost certain to declare itself primarily and chiefly by symptoms of cerebral disturbance. In accordance with this we find that such interference with the process of nutrition, as results from the retention in the blood of excretory products, declares itself by nervous symptoms, headache, giddiness, delirium, convulsions, and coma.

The same symptoms may be induced by defective supply of the nutrient fluid. No matter whether the nutrition of the brain be interfered with from before backwards, or from behind forwards, it declares itself by like symptoms.

By uræmia, therefore, we understand a condition in which nutrition is interfered with from behind forwards; a condition, in short, of tissue-asphyxiation. And by uræmic

symptoms we understand those nervous symptoms which must result from such asphyxiation of the cerebral tissue.

Coma.—If the cause which gives rise to delirium and convulsions be long enough in operation, or exist in a sufficiently marked degree, death must ensue. When such is the case, the fatal result is brought about by coma. This condition may, of course, exist in a more or less marked degree: the comatose symptoms may come on gradually, may be comparatively slight, and the patient may all through the attack be capable of being roused to a certain extent: from such a state of partial coma recovery is common. But when the coma is profound, and (preceded or not by convulsions) comes on rapidly, the case generally proves fatal.

Post-mortem examination of cases which prove fatal in this way discovers no constant local lesion or change in the intracranial contents competent to the production of such a result. There may in some cases be an appearance of congestion of the pia mater, or rather more than the usual quantity of subarachnoid fluid, with some degree of cerebral atrophy; but these appearances are far from general, and are never so marked as of themselves to offer a sufficient explanation, either of the nervous symptoms noted during l fe, or of the occurrence of death. It is to uræmia, to the retention in the blood, and action on the brain, of the products of tissue metamorphosis that death is attributed. The true cause of the coma we believe to be that which has been offered in explanation of the occurrence of the delirium and convulsions which so often usher it in—malnutrition of the brain, induced in the manner just explained in the case of convulsions.

That there is at work in the system an agency competent to the production of such a condition has, I think, been sufficiently shown. That malnutrition of the brain is competent to the production of such symptoms as those whose causation we have been investigating, there is no doubt. To what other cause can be attributed the convulsions, and even profound coma, which may follow the sudden diminution of the blood supply to the brain, consequent on compression of the carotids? To what else are

to be ascribed the same symptoms occurring as a consequence of profuse hæmorrhage? And how otherwise, than by defective nutrition of the nervous centres, can we account for the occurrence of like symptoms in exhausting diseases such as diarrhœa (especially in children with their susceptible nervous systems), and in that more slowly induced state of exhaustion which results from defective supply of food, or from actual starvation?

The most undoubted and most potent cause of such head symptoms as present themselves in the course of idiopathic fever is defective nutrition of the nervous centres. No matter how this defective nutrition is brought about; be it by compression of the large, or contraction of the minute, arteries; be it by loss of blood, or exhausting diarrhœa; be it by the cutting off at the threshold of the system of the materials requisite to the formation of blood, or by the consumption of the nutrient ingredients of that fluid by some foreign agency, while circulating through the system—by whichever cause produced, the result is the same, so far as the nutrition of the nervous centres is concerned; it is the same also so far as concerns the symptoms by which this malnutrition of the nervous centres declares itself. These symptoms are chiefly delirium, convulsions, and coma. The degree in which these occur depends partly on the nervous constitution of the individual, and partly (and in most cases chiefly) on the extent of the malnutrition from which the nervous centres suffer, and on the rapidity with which this malnutrition is developed.

In children, and in adults of delicate nervous constitution, serious head symptoms are induced by causes which produce comparatively slight effects on the nervous systems of more robust individuals: witness the occasional occurrence of convulsions, instead of only rigors and headache, at the onset of an inflammatory, or febrile attack—the tendency to the development of the so-called hydrocephaloid disease in children as the result of exhausting diarrhœa—and the readiness with which serious head symptoms are developed in those of insane or epileptic parentage.

The constitution of the individual, then, is an important

factor in the production of serious nervous symptoms in some cases in which their exciting cause is malnutrition of the nervous centres. The extent of this malnutrition and the rapidity with which it is induced are important factors in all. In other words, the more complete and the more rapid the production of the anæmic condition of the nervous centres, the more marked the nervous symptoms. In anæmia (or, more correctly speaking, spanæmia) of the brain, resulting from a slowly acting cause, such as improper and insufficient food, diarrhœa or other exhausting discharge, the head symptoms are slowly induced, and pass through the various stages of listlessness, languor, irritability, restlessness, mental torpor, and confusion, up to a state of wandering and delirium, from which the sufferer may gradually lapse into a state of more or less complete coma: the gradual development of the nervous symptoms coinciding with the slow production of the spanæmia. In the rapidly induced anæmia which results from profuse hæmorrhage, from sudden compression of the carotids, or from sudden spasm of the minute arteries of the brain, there is no time for the development of the slighter symptoms of defective nutrition which result from mere spanæmia: the deprivation of blood is so complete and so rapidly produced, and the consequent disturbance of the nervous centres so great, that it at once gives rise to well-marked convulsions and coma. So it is with the nervous symptoms of fever. These, we have seen, are due to impaired nutrition of the brain, resulting from the action of the contagium. The extent to which the brain is deprived of its nutriment, and the extent to which this deprivation declares itself in nervous symptoms, depends on the amount of contagium produced. When comparatively little is produced, there is a correspondingly slight interference with the nutrition of the brain, and the symptoms resulting therefrom are also slight. When there is a great and rapid propagation of contagium, there is an equally great and rapid deterioration of the nutrient fluid, a corresponding interference with the nutrition of the brain, and a consequently rapid development of serious nervous symptoms. Hence it is, that in mild cases

of fever, in which comparatively little contagium is reproduced, the participation of the nervous system in the general disturbance declares itself only by slight wandering; while in severe cases, in which there is a large reproduction of contagium particles, it declares itself by violent delirium, convulsions, and coma.

That there is during the course of the febrile attack very serious impairment of the nutrition of the brain is further evidenced by the mental, as well as bodily, state of the patient during the early weeks of convalescence. The mental faculties are indeed generally restored in a few days; but there is for a time, which varies according to the severity and duration of the febrile attack, a degree of listlessness and incapacity for mental effort, and an excitability of the emotional faculties, which sufficiently indicate that the brain has suffered seriously during the continuance of the fever. Sometimes the indications of cerebral weakness are very marked, and the patient may, for weeks, say and do things which, but for the preceding febrile attack, would be regarded as evidence of insanity.

There is, too, a form of post-febrile delirium to which Graves first prominently directed attention, which comes on after the patient has been convalescing satisfactorily for some days. While all is apparently going on well, the patient suddenly, and often without apparent cause, becomes violently delirious. This state generally continues for a few days, and then passes off: but it may persist for weeks; and Murchison alludes to two cases convalescent from typhus in which the maniacal excitement was so great, and so lasting, as to require temporary restraint in a lunatic asylum. This form of delirium is anæmic in nature. 'There is no evidence that either the fatuity or the maniacal attacks depend on softening or inflammation of the brain or membranes; they are attended not by fever or headache, but by anæmia and nervous depression, and are therefore benefited by sedatives and stimulants; and they are chiefly observed in cases where the primary fever has been characterised by great and protracted delirium, and where there has, no doubt, been an unusual degree of cere-

bral atrophy.'[1] They occur chiefly in those cases in which there has been great and protracted delirium during the primary attack, because such delirium occurs only in cases in which there is a large reproduction of contagium particles, and a correspondingly great interference with the nutrition of the brain.

The propagation of the contagium in the system gives rise, in the brain, to exactly the same effect which it produces on the muscles; allowance being made for such differences as must result from the difference in the nature and function of the brain and muscular system. In both there is produced a serious amount of malnutrition, from which neither recovers for a considerable time; which in the muscles give rise to weakness and loss of bulk, and in the brain to weakness and impairment of function, and such atrophy of the organ as is frequently found in fatal cases.

It is thus evident that all the nervous symptoms which occur in idiopathic fever, the rigor which ushers it in, as well as the coma which terminates it, and the mental weakness which follows it; the headache of the mild case, and the violent convulsions of the severe one, are all ultimately due to one cause, defective nutrition of the nervous centres, the more or less direct result of the propagation in the system of the contagium particles.

That one cause should be capable of affording a reasonable explanation of phenomena so varied is a strong argument in favour of its being the true agency which leads to their production. And the probability of its being so is greatly enhanced by the fact that this cause is not only operative, but is the primary agent, in the production of the phenomena of every case of fever.

That which causes the fever necessarily causes the individual phenomena which go to constitute that state. The nervous symptoms whose causation we have been investigating are part and parcel of the attack during whose course they occur; they are the evidence of the severity of the seizure, and are as much a characteristic feature of the case as are the high temperature, and scanty elimination of

[1] Murchison, *op. cit.* 2nd ed. p. 205.

urine, which are noted at the same time. Such being the case, it is but reasonable to attribute their occurrence to the same cause which, we have seen, gives rise to the so-called essential phenomena of the febrile state. The competence of this agency to produce them has, we think, been fully shown.[1]

[1] The great argument in favour of the view which regards the nervous symptoms of fever as of uræmic origin, and the chief objection to that which we have advanced as to their causation, is the occurrence of similar symptoms in advanced cases of Bright's disease.

Here it is found that the kidney disease leads to the retention in the blood of excretory products. Following, and evidently consequent on, such retention, serious nervous symptoms are developed. Naturally, the retention of the excreta is looked upon as the cause of the nervous symptoms, and so, no doubt, it is, but that is a bald and misleading statement of the facts of the case. There can be no question that retained excreta do produce disturbance of the nervous centres. The point of discussion is not their competence to do so, but the manner in which they act in the production of such symptoms.

Different views have been advanced in explanation of their mode of action. The demonstration by Christison (1829) of the presence of excess of urea in the fluids of the bodies of those who died of Bright's disease, led to the belief that the nervous symptoms which preceded death were due to the direct toxic action on the nervous centres of retained urea. It was found in time, however, that urea might be retained in, and even injected into, the circulation without producing disturbance of the nervous centres. Impressed with this fact, Frerichs advanced the view that the real toxic agent was carbonate of ammonia, produced by decomposition of urea in the blood. But the same objections have been urged against the capacity of carbonate of ammonia to produce such a result, which were previously urged against urea. Oppler, recognising the force of these objections, but still impressed with the view that retained excreta are somehow the cause of the nervous symptoms, attributes them to the retention in the nervous centres of the products of their own waste.

Owen Rees thought that some other cause than retention of excretory products, probably a watery condition of the blood, had something to do with their production.

Traube very ingeniously elaborated this view. He believed that the impoverished state of the blood, and the coincident occurrence of cardiac hypertrophy, led to the exudation of water through the coats of the minute vessels; that there was thus produced œdema of the central substance; that the capillaries and veins were pressed upon by this effusion; and that this pressure gave rise to anæmia of the brain. To this anæmic condition of the brain he ascribed the nervous symptoms. The great objection to this ingenious theory is that nervous symptoms are most common in that form of Bright's disease (the contracting granular kidney) in which œdema is least apt to occur.

Rommelære believed that the uræmic symptoms resulted from a combination of different causes, retention of excretory products, retention of

TYPHOID SYMPTOMS.

The sunken and depressed aspect of the patient, the moist clammy skin, the listless expressionless eye, the sordes-

water, and consequent blood impoverishment, and increased tension of blood vessels.

Dr. George Johnson 'assumes it to be indisputable that the nervous symptoms are the result of the blood being deteriorated, partly by diminution of its normal constituents, but chiefly by retention and accumulation of urinary excreta. There are two ways in which it is probable that the brain and its functions may be injuriously affected by this blood deterioration. First, the cerebral tissues, fed with poor and poisoned blood, may have their nutrition impaired, and may in various parts undergo structural changes, analogous to those which are often demonstrable in the texture of the retina. Second, it is probable that some of the cerebral symptoms, more especially those which come on and pass away suddenly, are directly due to temporary interruptions or hindrances of the circulation through certain regions of the brain, consequent on excessive contraction of the minute arteries. . . . It is in a high degree probable that uræmic vertigo, amaurosis, delirium, convulsions, and even coma, may in some cases be explained by partial or general cerebral anæmia, the result of excessive arterial contraction excited by the presence of impure blood.'

There can, we think, be little doubt that this is the true explanation of the mode of production of the nervous symptoms of Bright's disease. A consideration of the cases in which such symptoms are most apt to occur will render this more evident.

The form of Bright's disease in which nervous symptoms are chiefly noted is that which is associated with a small, red, granular kidney. The exact pathogenesis of this form of kidney disease has been matter of much discussion. On one point, however, all are agreed: the malady is not a local disease of the kidney, but a constitutional affection, whose most marked local manifestation is the production of renal mischief. There is decided impairment of health before, generally for some considerable time before, there is evidence of kidney disease: the characteristic feature of this constitutional derangement is an impoverished state of the blood. 'There is no disease of a chronic nature which so closely approaches hæmorrhage in its power of impoverishing the red particles of the blood' (Christison).

There is thus in operation, in that form of Bright's disease in which nervous symptoms are most common, the cause which of all others is most competent to produce functional disturbance of the nervous centres—cerebral anæmia. As the general constitutional derangement advances, the impoverished state of the blood becomes more marked: the renal disease likewise advances; and the already existing blood deterioration is increased by the retention in that fluid of excretory products. We thus have the process of nutrition interfered with in a twofold manner, just as we found it to be in bad cases of fever. There is a constitutional anæmic condition, producing defective nutrition of the nervous centres: and there is the

coated teeth and lips, the dry brown tongue, the feeble flickering pulse, the twitchings and subsultus, the low muttering delirium, the involuntary evacuations, sufficiently indicate the adynamic nature of that aggregate of phenomena to which the term 'typhoid state' is applied. This state is common to the advanced stages of various diseases; and in all it is attributed to one cause, retention in the system of excretory products. Such retention is assumed to be the cause of the typhoid symptoms in fever, because almost identical symptoms are noted in advanced cases of renal disease; because in fever, as in renal disease, there is, when such symptoms occur, excess of urea in the blood; and (perhaps chiefly) because no other explanation is forthcoming.

All the phenomena of the specific fevers are directly or indirectly results of the propagation of their poisons in the system. The typhoid symptoms are no exception. To say that a fever patient is suffering from typhoid symptoms, is merely a short and convenient way of saying that there

presence in the blood of retained excreta, interfering with, and impeding, the normal retrogressive changes.

The other form of Bright's disease in which serious nervous symptoms are most apt to occur is the acute inflammatory form, occurring either *per se*, or grafted on to one of the chronic forms. Serious nervous symptoms are apt to occur under such circumstances because, as a consequence of the renal mischief, there is produced a sudden and rapid accumulation of excretory products in the blood, and because such rapid accumulation is apt, in the manner explained by Dr. Johnson, to cause sudden spasm of the minute arteries of the brain. Here, too, the nervous symptoms are due to cerebral anæmia, rather than to any direct toxic action on the nervous centres of retained excreta.

A careful consideration of the phenomena which precede and accompany the development of the nervous symptoms of Bright's disease thus leads to the conclusion that they are due, not to any direct irritant action on the nervous centres of retained excreta, but to faulty nutrition of these centres—the same cause to which we have ascribed the occurrence of like symptoms occurring in the course of the eruptive fevers.

The typhoid symptoms occasionally noted in advanced cases of Bright's disease own a similar causation.

Retained excreta do not act directly on the brain substance; they simply render impossible the continuance of the normal tissue-changes. Their presence in the blood puts a stop to the changes which normally take place in the tissues, in the same way, and as effectually, as an atmosphere of carbonic acid puts a stop to the changes which normally take place in the lungs.

are great disturbance and depression of the nervous centres, as indicated by the muttering delirium, the twitchings of the muscles, the incontinence of urine, and the generally sunken and depressed aspect; and that there is threatened failure of the heart's action, as indicated by the feeble flickering pulse, the almost or altogether imperceptible cardiac impulse, and scarcely audible first sound; that, in short, the patient is in imminent danger, and that death is threatened in a twofold manner, by coma and by asthenia —by failure of cerebral, and by failure of cardiac action.

Coma occurring in fever is due mainly to defective nutrition of the nervous centres. The coma which supervenes in the typhoid state is due to the same cause, but presents in its development certain differences due to the co-existence of other indications of danger to which we must for a moment direct attention.

When death in fever is threatened by coma alone—when the danger is from the head symptoms, and not from failure of the cardiac action, or from pulmonary or other complication, the symptoms of coma are preceded by marked, and often violent, delirium, which may even culminate in well-marked convulsions. Be it particularly noted, however, that, with such symptoms, there are not the same indications of intense depression which obtain in the typhoid state. Instead of being sunken and almost motionless in bed, as in the typhoid state, the patient, until death is imminent, is restless, and even making efforts to get up, in which an often troublesome amount of muscular power may be displayed: delirium, instead of low and muttering, is acute and violent; the skin, instead of being moist and clammy, is hot and dry; the pulse is rapid, but wants the feeble character of the typhoid state; the heart's impulse is fairly perceptible, and there is no threatened failure of its action. The danger is from the head symptoms, and from them alone, and, therefore, the coma is uncomplicated by other indications of danger than those referable to the nervous centres.

But in the typhoid state this is not the case. Death is threatened as much by asthenia as by coma; and it is the

combination of these two different modes of dying which imparts to that state its distinctive peculiarities. The presence of asthenia is sufficiently indicated by the feeble flickering pulse and failing cardiac action. It is the presence of this asthenia which takes from the nervous symptoms their sthenic character, and gives to the patient the sunken and depressed aspect which characterises the typhoid state. Be the symptoms of asthenia present or absent, however, the nervous symptoms are due to one and the same cause, defective nutrition of the nervous centres, consequent (*a*) on the consumption by the contagium particles of the materials necessary to the nutrition of the brain, and (*b*) on the retention in the blood of excretory products.

Whether, then, in a bad case of fever the patient becomes violently delirious, convulsed and comatose, or lapses into the typhoid state, would seem to depend on the absence or presence of asthenia—on the absence or presence of symptoms of threatened failure of the heart's action. To a certain extent this is true; but the statement is rather bald, and requires further explanation. We have, therefore, to consider why it is that coma seems to play a more constant part in the tragedy than does asthenia, and what is the difference between the mode of production of simple coma, and of that which occurs in combination with asthenia in the typhoid state.

To this question there is a twofold answer. In the first place, all other things being equal, the occurrence of typhoid symptoms indicates a severer attack, a larger reproduction of contagium particles, than does the occurrence of head symptoms alone; it being apparent that, always *cæteris paribus*, a larger reproduction of contagium particles would be required to impair all the vital energies than would be requisite to impair only those of the brain. To put it otherwise: the brain requires and receives a much larger quantity of arterial blood than any other organ of the body. Requiring so large and so constant a supply of nutriment, it follows that the brain must, more than any other organ, suffer from such a deterioration of the nutrient fluid as that to which

the propagation of the contagium gives rise. We accordingly find that symptoms referable to the nervous system are among the earliest and most constant indications of the existence of fever. Now, if the propagation of the contagium reach, but do not exceed, the point necessary to produce the degree of cerebral malnutrition requisite to the production of comatose symptoms, we may have those symptoms developed without other or further indications of urgent danger: but if this point be exceeded, or if any cause of cardiac depression comes into play at the same time, then signs of defective action of that organ make their appearance; symptoms of asthenia are developed *pari passu* with those of coma; and we have induced that aggregate of phenomena to which the term 'typhoid state' is applied; a state which is simply one of great depression of all the vital energies; simple coma being one of great depression of only the nervous energies.

We have said that, *other things being equal*, typhoid symptoms indicate a larger reproduction of contagium particles than does the occurrence of head symptoms alone. But other things are not always equal; and it is often to some constitutional peculiarity of the individual that is due the special prominence of symptoms referable to this or that organ. It is well known that those of delicate nervous organisation, and those who, from hereditary or other predisposition, are liable to head affections, are, when seized with fever, more likely to have serious nervous symptoms than those in whom no such predisposition exists. So also those in whom, from age or other cause, there is defective power, or impaired vigour, of the muscular walls of the heart, are more likely to suffer seriously from asthenia than those in whom the cardiac action is vigorous and unimpaired. Those in whom these conditions are combined, and those in whom, even without any special predisposition, the quantity of contagium produced is so great as to give rise, at one and the same time, to the requisite degree of malnutrition of the brain and heart, suffer from that combination of coma and asthenia to which the term 'typhoid state' is applied.

The typhoid symptoms of fever are, therefore, due to

failure of all the vital energies, such as must result from that derangement of the whole process of nutrition to which we have seen that the propagation of the contagium in large quantities gives rise.

The uræmia by which they are accompanied tends to make the typhoid state more marked, but is not the original cause of its occurrence. It acts here in the same way as we saw that it did in the production of the nervous symptoms, aiding the cause already in operation, and increasing the already existing depression.

Such is the mode in which metabolic fever tends to prove fatal. Death is either by asthenia or by coma—by failure of cardiac or failure of cerebral function, induced in the manner explained. Post-mortem evidence tends but to confirm this view. This evidence we must briefly consider.

THE CHANGES NOTED AFTER DEATH.

As a rule, these are slight, and bear little relation to the severity of the symptoms noted during life. Even in those cases which present the most marked symptoms during life, and which prove fatal, apparently by the severity of such symptoms, there is found no local lesion sufficiently constant and important to give rise to such a result.

The chief post-mortem changes are those which occur in the brain and in the heart.

In the brain the chief changes noted are (*a*) some venous congestion both of the brain and its membranes, (*b*) some increase in the quantity of intracranial fluid, and (*c*) atrophy of the brain itself. None of these changes is constant; and pathologists agree that neither the amount of congestion, nor the amount of effused serum, bears any relation to the severity of the symptoms.

The congestion is most marked in cases in which there has been some obstruction to the pulmonary circulation: it is then partly due to such obstruction; but it often exists independently of such a cause, though seldom to any marked extent; it may be slight in cases which, during life, presented marked nervous symptoms.

The quantity of fluid effused into the ventricular and subarachnoid spaces also varies; and it has been abundantly proved by the observations of Reid, Jenner, Jacquot, Barrallier, &c. that the nervous symptoms bear no relation to the quantity of fluid found in these localities.

It is indeed very probable that the increased quantity of serum noted in connection with cerebral atrophy is, as Murchison remarks, 'merely thrown out to fill the space vacated by brain.'

The principal intracranial change observed in connection with the head symptoms of fever is atrophy of the brain—diminished bulk of the cerebral substance. This, therefore, is the change for which we have chiefly to account. The cause most likely to give rise to such a change in the brain is defective nutrition of that organ—insufficient supply of the material required for its nutrition and the maintenance of its bulk. Diminished bulk of brain tissue, with increased serosity, is a recognised result of chronic wasting disease; and defective nutrition, such as occurs in these ailments, is the only recognised cause of cerebral atrophy. That this agency operates in the specific fevers has already been shown. We have seen that many of the most striking phenomena of the febrile state, and notably the nervous symptoms, result from the propagation in the system of an organism which, in its growth and increase, not only consumes the material requisite to the nutrition and building up of the tissues, but causes also a coincident increase in their retrograde changes. Acting on the muscles, this agency produces the wasting which forms so prominent a feature of idiopathic fever: acting on the brain, it induces a like acute inanition and consequent waste of brain tissue. The cerebral atrophy, then, which forms the chief of the intracranial changes noted after death from idiopathic fever, results (as might on *à priori* grounds be anticipated) from the same cause which gives rise to the nervous symptoms noted during life—defective nutrition, and increased disintegration, of the brain substance, consequent on that disturbance of the process of nutrition to which the propagation of the contagium gives rise.

The changes which take place in the central organ of the circulation during the course of idiopathic fever have been studied chiefly in connection with typhoid and typhus fevers. They were first described by Laennec,[1] and afterwards more accurately by Louis and Stokes. The most prominent of the changes noted is a softened and friable condition of the heart, chiefly its left side. When very marked, and affecting the whole organ, Louis describes the heart as being 'very flaccid, so that in many cases it had no precise form, but, like a wet cloth, retained any shape into which it might happen to be placed. Its substance had very little power of cohesion, and was easily torn, or penetrated by the finger.'[2] Stokes described a case in which the softening was so great that 'when the heart was grasped by the great vessels, and held with its apex pointing upwards, it fell down over the hand, covering it like the cap of a large mushroom.'[3] These, of course, are extreme cases; but the observations of all pathologists show that such softening occurs to an appreciable extent in a large number of cases of idiopathic fever.

Regarding the nature of this softening there has been some difference of opinion. Laennec looked upon it as simply part of the general softening of the muscular fibres noted in cases of idiopathic fever accompanied by putridity of the blood. Louis, on the other hand, maintained that the cardiac softening was altogether peculiar, and that 'no such lesion was found in any other muscular organ, the voluntary muscles maintaining their normal consistence and colour.'[4]

Stokes adopted Louis's view, and pointed out the signs by which the softening could be detected during life, and the important indications as to treatment which such signs gave.

Rokitansky regarded the softening as 'a mere symptomatic and simple diminution of consistence, not depending on

[1] *Traité de l'auscultation méd.*

[2] Louis, *Recherches sur la Gastro-entérite*, tome i. p. 330 (1829).

[3] *Stokes on the Heart*, p. 373 (1854); and *Lectures on Fever*, p. 222 (1874).

[4] *Op. cit.* tome i. p. 333.

any disturbance of texture.'[1] While Murchison[2] and Joseph Bell[3] describe the fibres of the softened portion as having lost their natural striated appearance, and as undergoing granular, fatty, or waxy changes. My own observations accord with those of Murchison and Bell.

Such is the cardiac lesion noted in many cases of idiopathic fever. It consists in a softened and friable condition of the cardiac walls, and in granular, fatty, or waxy change of the muscular fibres, and has for its most prominent symptom an enfeeblement of the cardiac power, which may be so great as to cause death by failure of the heart's action.

The chief points to be noted regarding the change which takes place in the heart are:—

1. That signs of its occurrence are not observed till the fever has been in existence for some time.
2. That the signs of cardiac feebleness, when once noted, increase with the progress of the fever.
3. That such signs are most decided in cases of a markedly typhoid type.
4. That they speedily disappear after the cessation of the fever.
5. That complications which prolong the illness after the cessation of the fever do not prevent recovery of the heart's tone.
6. That the softening noted after death is always more marked on the left than on the right side of the heart; and in the ventricles than in the auricles.
7. That it is more marked in cases which prove rapidly fatal than in those in which the fatal issue is more tardy. (Louis.)
8. That the normal striated appearance of the fibres of the softened portion is indistinct or imperceptible, and is replaced by granular, waxy, or fatty change.

Regarding the mode of production of this change in the heart different hypotheses have been advanced, but no

[1] *Pathol. Anat.* Sydenham Soc. translation, vol. iv. p. 171.
[2] Murchison, *op. cit.* p. 259.
[3] *Glasgow Med. Journ.* 1860.

satisfactory explanation has been given. Laennec regarded it as a putrid softening, but the inaccuracy of this view has been demonstrated. Louis advanced no explanation more definite than the hypothesis that the cause which gave rise to it was something the reverse of inflammation, 'une cause de lésions opposée à l'inflammation.' Since then our knowledge on this point has made little advance.

The view generally adopted is that of Louis, that the change in the heart is altogether peculiar, and distinct from that which exists in the voluntary muscles. The contrary doctrine of Laennec, that the changes in the heart and muscles were similar in nature, seems to merit more consideration than it has received. Laennec was, no doubt, in error when he attributed the softening to a putrid condition of the blood; but it does not follow that he erred in regarding the changes in the heart and voluntary muscles as similar in nature. He might err on one point without being wrong in all. Louis demonstrated beyond a doubt the inaccuracy of Laennec's etiology; but regarding the state of the voluntary muscles, all that he said was that they were of natural consistence and colour. Now in this there can be no doubt that Louis was in error; the voluntary muscles do not preserve their natural consistence and colour in all cases in which the heart is softened. Laennec and Stokes have both recorded cases in which they were of soft and gluey consistence; while all those who have made frequent post-mortem examinations in cases of typhus and enteric fevers know that the muscles often present a less than natural degree of coloration. They are frequently also darker than normal, but that is when there has been some obstruction to the pulmonary circulation.

Of late years the condition of the muscles has been inquired into with greater accuracy; and it has been demonstrated, more especially by the observations of Murchison[1] and of Zenker,[2] that during the course of idiopathic fever the fibres of the voluntary muscles undergo a change

[1] Murchison, *op. cit.* 1st edition, 1862.

[2] Zenker, *Ueber die Veränderungen der willkührlichen Muskeln im Typhus abdominalis*, 1864.

(waxy, fatty, or granular) similar to that which is noted in the minute structure of the softened heart. With such a fact before us, we cannot fail to see that, to some extent, the views of Laennec were possibly more accurate than those of Louis; and that the change which takes place in the heart may, after all, be similar in nature to, and due to the same cause as, that found in the voluntary muscles.

This change is essentially one of intense and rapidly induced enfeeblement. It has already been shown that the cause to which we ascribe all the phenomena of idiopathic fever, the propagation of the contagium, produces marked disturbance and even atrophy of the brain, and great wasting of, and interstitial change in, the voluntary muscles. If competent to produce these, there is no reason why it may not produce such a change as that whose causation we now investigate. We believe that such is the mode of production of the cardiac softening; that it results from coincident defective nutrition and increased disintegration of the muscles of the heart: the defective nutrition being due to the consumption by the contagium particles of the nitrogen and water which ought to go to build up the cardiac muscles; the increased disintegration being due to the continuance, in even an increased degree, of those changes which result in their disintegration.

But, it may be asked, if the same cause give rise to the changes in the heart and voluntary muscles, why are the results not identical? Why is the heart only softened, and not markedly diminished in bulk, as are the voluntary muscles? To understand aright the reason for this difference we must bear in mind that, though similar in structure, the heart and voluntary muscles have very marked points of difference. We know, for instance, that the heart does continuously, and without any period of rest, an amount of work which no voluntary muscle could do for more than a short time; and that, in its innervation, formation, mode of action, and, indeed, in every respect except in the appearance of its fibres, it is essentially different from voluntary muscle. In no way is this difference better indicated than by the fact that while within the limits of

health the bulk of voluntary muscles may vary much, that of the heart remains the same: it is not liable to vary except as the result of some morbid or abnormal agency. That under these circumstances the pathological changes which take place in the heart should differ from those which occur in voluntary muscles (even though both may result from a like cause) is no more than might reasonably be expected. The circumstances of the heart and of the voluntary muscles are so different, that like results in each could scarcely be looked for. Such rapid loss of bulk as takes place in voluntary muscles could not occur in the heart without leading to fatal asthenia. That there should be some provision against such a result is what might be expected. We know as a fact that causes which in the voluntary muscles produce loss of bulk do not have a similar effect on the heart. It need not, therefore, surprise us to find, that while the action of the fever poison causes in the voluntary muscles granular or waxy change with loss of bulk, it produces, in the cardiac muscles, similar changes, with softening and friability of their substance.

To one point in which the condition of the heart and of the voluntary muscles differs in fever I would direct special attention. The heart acts with more than normal rapidity: the voluntary muscles are more than normally quiescent. While there is going on in both that deranged tissue-action to which the propagation of the contagium gives rise, the heart is called upon to do more work than natural, the voluntary muscles less.

Such a marked difference in their respective conditions could scarcely fail to lead to a difference in the results noted in the heart and muscles as a consequence of the fever. Both being subjected in a like degree to the enfeebling action of the contagium, no great difference in the results noted could reasonably be expected, if the heart and voluntary muscles were in all respects similarly situated. But with such an important difference as that which has been indicated—with the heart subjected to an abnormal amount of wear and tear, in addition to those derangements of nutrition which are common to it and the voluntary muscles,

it is all but inevitable that there should be noted in it an exaggerated degree of those changes which occur more or less in all striated muscular fibre as a result of the action of the fever poison.

We accordingly find that the diminished striation, and the granular, fatty, and waxy degeneration, which constitute these changes, are more marked in the overworked heart than they are in the underworked voluntary muscles. The softness and friability which form the coarser and more striking indications of the change which takes place in the fibres of the heart are not altogether wanting in the voluntary muscles of those cases in with such change is marked in the cardiac walls: but the microscopic changes which are the essential and more accurate indications of its existence are more constantly observed.

That the increased call which is made upon the heart has some influence in producing the prominence of the changes observed in that organ, is evidenced by the fact that these changes are more marked in the left than in the right heart, and in the walls of the ventricles than in those of the auricles. Were they the result of any direct toxic action of the fever poison, or of a putrid condition of the blood, the softening would be general, and equally marked in all the fibres of the heart. The only reason that can be assigned for the greater involvement of the ventricles than of the auricles, and of the left than the right ventricle, is that the ventricles do harder work than the auricles, and the left ventricle harder work than the right. Those striated fibres which have most work to do, suffer most from the combined influence of defective nutrition and increased disintegration, and give the most decided evidence of so suffering. Hence the walls of the left ventricle are always more soft and friable than those of any other part of the heart: and hence also the changes which take place in striated muscular fibres during the course of idiopathic fever are always more marked in the cardiac walls than in the voluntary muscles.

The other *post-mortem* changes found in fatal cases of idiopathic fever are an enlarged and hyperæmic condition of

the liver and spleen, hypostatic congestion of the lungs, and some congestion of the kidneys. As a necessary result of increased metabolism all these organs are called upon to do more work than natural; while this call is being made they suffer from defective nutrition, in common with the rest of the body. This combination of events leads to lowered vitality, to strain and fatigue, and with increased rapidity of the blood flow, ultimately to congestion.

Such is the explanation which the germ theory of disease offers of the causation of the specific fevers, and which the metabolic theory of fever offers of the mode of production of the phenomena of fever as these present themselves at the bedside and in the post-mortem room.

The phenomena hitherto considered are common to the specific fevers. In not one of these phenomena is there anything by which we can satisfactorily distinguish one form of fever from another. Except relapsing fever, there is not one of the specific fevers in which the course of the general symptoms can be said to form the leading characteristic of the disease. That which imparts to each of them its distinctive features is not so much any peculiarity of the febrile symptoms, as the occurrence of local lesions. The most characteristic feature of small-pox is its eruption; of scarlatina the eruption and sore throat; of measles the eruption and accompanying irritation of the mucous membrane of the eyes and respiratory passages; of typhoid fever, the bowel lesion; of typhus, the rash; of cerebro-spinal fever, the meningeal affection. To these local lesions we must turn our attention: for in no clinical record may they be omitted.

THE OCCURRENCE OF CHARACTERISTIC LOCAL LESIONS.

That the local lesions of the specific fevers form part and parcel of the maladies during whose course they occur there can be no doubt; they are as constant in their

occurrence as the febrile symptoms, and much more characteristic.

That a connection exists between them and the specific properties of the contagia is also certain. During the propagation of each contagium there is developed a special local lesion, which is never observed under any other circumstances. The eruption of small-pox is never due to any other cause than the presence in the system of the poison of that disease. Nothing but the poison of enteric fever produces the bowel lesion characteristic of that malady. The eruptions of scarlatina, and of measles, are always due to the poisons of these maladies, and never result from any other agency. The presence of the contagium in the system is, doubtless, the cause which gives rise to the local lesion. How does it produce such a result?

There are two possible modes of action.

(*a*) It may be that the contagium acts in the production of the local lesion, in the same way as ordinary medicinal and poisonous agencies act in the production of the local effects to which they give rise: or (*b*) it may be that its action in this respect bears an intimate relation to its organic development, and is altogether peculiar.

Either view may be correct. To determine which is so, we must carefully weigh the evidence for and against each.

That many poisonous and medicinal agencies exercise a special irritant action on certain organs is a recognised fact in toxicology and therapeutics. No matter by what channel they are introduced into the system, arsenic acts on the stomach and rectum, cantharides on the bladder, and ergot on the uterus.

This predilection of certain ordinary poisons for particular organs forms the main argument in support of the opinion which ascribes the local lesions of the eruptive fevers to a similar action on the part of the poisons which give rise to these maladies. And there can be no question as to the cogency of the argument. There is no reason

why contagia may not so act. Even on the view that they are living organisms, there is no reason why their peculiar local action should not be due to some active principle, bearing to contagia the same relation that cantharidine does to the *cantharis vesicatoria*, or ergotin to ergot of rye.[1]

It is an argument against, though not destructive of, this view, that in none of the specific fevers has any such principle ever been separated; and that the poisons of such of these diseases as can be experimented with have never been found to exist, except in a particulate and indiffusible form.

There are, however, many points in which a very great difference is found to exist between ordinary poisons and those which give rise to the eruptive fevers. They may here be presented in a tabulated form.

Circumstances to be noted in connection with the local effects of ordinary poisons.	*Circumstances to be noted in connection with the local lesions of the specific fevers.*
1. A definite and appreciable quantity of the	1. The minutest possible quantity of the poison

[1] That the contagia of the specific fevers act, in the production of their local lesions, like ordinary poisons, is the view held by the opponents of the germ theory, and advocated by them in opposition to that theory. (Murchison, *Transactions of Pathological Society of London*, 1875.) There is, however, no necessary antagonism between this view of the mode of action of contagia and the theory which regards them as living organisms. This latter may be quite true: but its being so does not negative the idea that the poisons of the eruptive fevers may produce their special local lesions in the same way as arsenic acts on the stomach and rectum, cantharides on the bladder, and ergot on the uterus. The fact that some dead organic and inorganic agencies exercise a special irritant action on certain parts of the body, no matter how they gain entrance to the system, shows that a living organism is not essential to the production of such a result; and that the occurrence of a peculiar local lesion in the eruptive fevers is not, *per se*, proof that the poisons of these diseases are living organisms. On the other hand, it does not militate against that view. The belief that contagia act like ordinary poisons in producing local lesions is not inconsistent with belief in the germ theory. It is simply antagonistic to the view which regards these lesions as intimately related to the organic growth of the contagia, and altogether peculiar.

poison is requisite to the production of any effect.	suffices to produce its full effect.
2. The severity of the symptoms, and the extent of the local mischief, bear a direct relation to the quantity of poison taken into the system.	2. The severity of the symptoms, and the extent of the local lesion, bear no relation to the quantity of poison taken into the system.
3. In all ordinary poisons a small and varying, but always appreciable quantity may be received into a susceptible system without producing effect.	3. The least particle taken into a susceptible system suffices to produce the full effects of the poison.
4. The quantity which exists in, and is eliminated from, the system, is never in excess of that which was received.	4. The quantity which exists in, and is eliminated from, the system, is always very greatly in excess of that received.
5. The system being allowed to recover from its effects, the same action may be produced over and over again.	5. One attack of the specific fevers confers, as a rule, immunity from a second.
6. By the gradual and regular administration of many poisons the system may become so habituated to their presence, that a large quantity may be taken with impunity.	6. In the specific fevers no such thing is possible: there is either a distinct action, or none at all; and a small dose is as potent as a large.
7. The poison continues to act so long as it exists in sufficient quantity in the part on which its action is manifested.	7. The local lesion shows signs of improvement, and the poison ceases to produce its special effects, while much of it still exists in the system.

The existence of so many points of difference creates a

broad line of demarcation between ordinary poisons and those of the specific fevers, and renders it probable that they differ in their mode of action.

The peculiarities presented by the poisons of the specific fevers are readily explained on the view that they are living organisms, which are largely propagated in the system during the course of the maladies to which they give rise, and whose action as poisons is intimately connected with their organic development. We have seen that there is good reason for holding this view: and for further holding that the general symptoms common to the specific fevers result from the propagation in the system of millions of minute organisms: we have further seen that their local lesions form, not only essential, but also the most distinctive features of these fevers. It is, therefore, probable that these local lesions also bear some relation to the growth and propagation of the germs. That lesion which is specially characteristic of a disease must be associated with the action of the poison which specially produces the disease. Certainly it is incumbent upon us to consider this hypothesis before we commit ourselves to any other.

The question which presents itself for consideration is whether or not the propagation in the system of the poisons of the eruptive fevers is capable of causing the local lesions characteristic of these maladies.

The primary and essential condition of the local lesion of each of the eruptive fevers is an increased afflux of blood to the affected part. In some cases it goes no further; but in others it goes on to congestion, inflammation, suppuration, and even sloughing: in all, however, the primary condition is one of hyperæmia. Is there any cause capable of giving rise to such localised hyperæmia?

We have found in the growth of the contagium particles in the minute structure of the tissues, and in the appropriation by them in that locality of the nutrient ingredients of the blood, the explanation of the general increase of the blood flow, which characterises the febrile state: we have found, in short, that this increased flow of blood results from the growth of the contagium as an organism.

But the contagium is also a parasite; and as such, requires a special nidus for its propagation. Wherever situate, the nidus is necessarily supplied with blood, and must be reached by the contagium particles which that fluid carries along with it: through its blood it affords to these particles the nitrogen and water requisite for their organic growth: but in addition, it is also the seat of that peculiar action which the term 'fecundation' implies. What takes place in the nidus, therefore, is the same action as goes on in all parts of the body, *plus* that which necessarily attends the process of fecundation. In the absence of any definite knowledge on the subject, it would be natural to suppose that the fecundation of an ovum or seed required a greater expenditure of force than the mere maintenance of its vitality—that a greater degree of energy was required to start those forces which the existence of life implies, than was requisite to keep them a-going after they had been set in motion. And we know from observation that such is the case. The immediate consequence of the fecundation of the ovum of one of the higher animals is an increased flow of blood to it, and increased vascular excitement of the maternal organs concerned in the process. During the period of germination and flowering of some plants, the increased action which accompanies the process may be so great as to cause a decided rise of the temperature of the part in which the action occurs. So great is this rise in some cases (especially in some of the araceæ) that the heat produced may be felt by the naked hand. I do not for a moment mean to say that the process which takes place during the fecundation of the contagium particles is the same as that which occurs in the impregnation of ova and the germination of seeds; I merely say that it bears to it sufficient analogy to warrant us in founding an argument thereon. Contact with its special nidus is as essential to the development of the ovum or germ of a parasite as is contact with the seed of the male to the ova of the higher animals, or contact with the pollen to the pistils of plants.

The contagium particles, as parasites, find in their nidus

something which is essential to their fecundation, and without which they cannot be reproduced. The poison of any of the specific fevers may be introduced into the system, but unless it reach this second factor in its nidus, it is not propagated, as will be more fully shown when considering the question of immunity from a second attack. There certainly takes place in the nidus an action which takes place nowhere else, and which must be accompanied by some evolution of force. From what is observed in the case of higher organisms, we may conclude that this evolution of force is likely to be accompanied by increased activity in, and increased vascularity of, the part in which the action occurs. Increased vascularity is the primary and essential condition of the local lesion of each of the specific fevers. The part so affected is the nidus in which the contagium finds its second factor: and the localised hyperæmia which constitutes the local lesion is the necessary result of the action which accompanies the fecundation of the contagium particles. Such is the connection which seems to obtain, on the one hand, between the specific properties of the contagium and the local lesion; and, on the other hand, between this local lesion and the nidus of the parasite. The seat of the local lesions of the eruptive fevers is the nidus in which their poisons, as parasites, find the second factor essential to their propagation; and the hyperæmia which constitutes the local lesion is the necessary accompaniment of the hyperaction which the term 'fecundation' implies.

This view of the nature and mode of production of that lesion serves better to explain the phenomena under consideration than does the alternative view that the lesion results from an action similar to that by which ordinary medicinal and poisonous agencies produce their local effects.

In keeping with this view, the poisons of the specific fevers, the germs which cause them, ought to be most abundant in the seat of these lesions. And so we find it to be. The poison of small-pox, for instance, is most abundant in the pustules; that of typhoid fever in the stools.

THE DIFFERENT DEGREES OF CONTAGIOUSNESS OF THE SPECIFIC FEVERS.

The usually accepted view of the mode of action of the poisons of the specific fevers is that they are propagated in the blood, and find in that fluid all the materials requisite to their propagation and morbific action. On this view of the matter all the specific fevers ought to be equally contagious. But this is notoriously not the case. All experience shows that small-pox, scarlet fever, measles, and typhus fever are very contagious; while typhoid fever and cerebro-spinal fever are so little so, that many authorities say that they are not contagious at all. This is a diversity of result which cannot be explained on any view which regards the blood only as the field in which the contagium is reproduced; but is readily explained on that which accords to each a special localised nidus.

The contagiousness of a given fever depends on two things: first, on the readiness with which the contagium passes into the surrounding atmosphere from the bodies of those suffering from it; and second, on the readiness with which it reaches its second factor in the systems to which it gains entrance.

In considering this question we have, therefore, to take into account the part played both by the giver and the receiver of the contagium.

The giver. It needs no argument to show that the quantity of contagium in the atmosphere must play an important part in determining the spread of a contagious disease. The more numerous the contagium particles in the atmosphere of a room, the greater the chance of one or more of these particles being inhaled by those who breathe that atmosphere. The question which we have to consider is, why this chance seems to vary so much in the different specific fevers: why, for instance, an unprotected person cannot be for any length of time in the same room as a sufferer from small-pox without contracting the disease; while an equally unprotected person runs so much smaller

a risk in the case of typhus; and why, in the case of typhoid fever, he runs scarcely any risk.

On the view which has been advanced as to the important part played by the second factor, all this is very readily explained. We have seen that the seat of the local lesion is also the seat of the second factor, and of that fecundating action which follows contact of the contagium with its second factor, and results in its propagation. Contact with the second factor is essential to the fecundation of the organisms; and only those organisms which have been thus fecundated, grow, and produce the phenomena of disease. This fecundating action is constantly going on in the seat of the local lesion, to an extent which is directly as the amount of the second factor which exists therein. The local lesion is, therefore, the locality in which the contagium particles are likely to be most abundant: and we know from experience that such is the case.

The contagium being most abundant in, and most freely given off from, the local lesion, it follows that the contagiousness of each of the specific fevers must, to some extent, depend on the seat of this lesion. If this be on the cuticular, or respiratory surface, as in small-pox, measles, and scarlet fever, the contagium will readily and freely pass into the surrounding atmosphere, and every facility be afforded for its inhalation by those in the neighbourhood of the sufferer. If the local lesion be so seated that the emanations or discharges from its surface do not readily reach the atmosphere, as in typhoid fever and cerebro-spinal fever, there will be little chance of the air being contaminated, and an equally small chance of the contagium being inhaled by those who breathe this air; and the disease, though communicable in the strict sense of the term, will not be contagious in the ordinary sense of the word; though cases are recorded which sufficiently show that both typhoid and cerebro-spinal fever may sometimes be due to contagion.

The contagiousness of a given fever depends, then, so far as the giver of the contagium is concerned, on the quantity of contagium which passes off from his body into

the surrounding atmosphere in a given time: and that depends very much on the seat of the local lesion. The seat of the local lesion thus becomes an important agency in determining the degree of communicability of the particular form of fever in connection with which it occurs.

That fever in which the largest surface of local lesion is exposed to the atmosphere will, *cæteris paribus*, be the most contagious. Hence we find that such diseases as small-pox, scarlatina, and measles are very contagious; while typhoid fever, with its half-concealed local lesion, is very slightly so; and cerebro-spinal fever, with its wholly concealed lesion, is so seldom communicated from the sick to the healthy, that the majority of those who have studied the natural history of the disease have come to the conclusion that it is not contagious.

The receiver. He, too, exercises an important influence in determining the readiness with which he takes a given contagious fever. This influence is generally recognised, and is usually referred to under the vague term of 'individual susceptibility.' But to give it a name is not enough. What we have to do is to explain what individual susceptibility really is.

We have seen that the contagium, the first factor in the production of the eruptive fevers, is *per se* impotent for evil; and that it may be introduced into the blood without giving rise to any deleterious effects, unless it come in contact with its second factor; the *rapprochement* of these two being essential to the production of disease. In the varying degrees in which this second factor exists in different individuals, and in its greater or less diffusion over the system, we find the explanation of the varying degrees of susceptibility to the action of a given contagium presented by different people. Each contagium has its own peculiar second factor; each second factor has its more or less localised seat (the nidus of the parasite). According as this seat is more or less localised, it will be reached by the contagium circulating in the blood with more or less difficulty: and directly as the readiness with which the first factor reaches the second will, *cæteris paribus*, be the

contagiousness of the malady to which it gives rise. If widely distributed, and readily got at through the circulation, the disease will be very contagious: if confined to narrow limits, and with difficulty reached through the circulation, it will be slightly so. That which determines the degrees of contagiousness of each of the specific fevers, so far as the receiver is concerned, is simply the facility with which the first factor reaches the second through the circulation.

Here illustration will serve better than argumentation. For this purpose we shall take one of the most and one of the least infectious of the specific fevers, small-pox, and typhoid fever.

In small-pox the second factor is widely distributed over the skin, and to a less extent over the mucous membrane of the mouth and throat. Of what it consists we have no accurate knowledge; but it suffices for our present purpose to know that it is intimately connected with, and widely distributed over, the skin. A small-pox germ being inhaled, passes through the lungs into the circulation, and is sent along with the general column of blood. It will do no harm unless it come in contact with its second factor; and it is quite possible (and, no doubt, frequently does happen) that it may make the round of the circulation once and again, and may ultimately pass out through some eliminating organ, without entering a cuticular vessel, and, therefore, without doing harm. The extent of the cuticular surface is so great, however, and the number of vessels which go to it so numerous, that the chances are against the probability of the contagium circulating for any time with the blood without entering one of these: if it do so, it almost certainly comes in contact with its second factor, reproduces other germs, and so gives rise to small-pox.

There are one or two curious facts in the history of small-pox which are better explained on this than on any other hypothesis.

It is a fact, for instance, that in inoculated variola the period of incubation is shorter than in the natural disease.

On no view which regards the blood only as the seat of all the changes which take place can this fact be explained. The contagium gains entrance to the circulation as rapidly when taken in by the lungs as when it is inserted under the skin; the symptoms to which it gives rise ought, therefore, on the view that the blood is the seat of its action, to be as speedily developed in the one case as in the other.

Two agencies tend to shorten the period of incubation of inoculated variola—agencies whose operation is readily explained on the view advanced regarding the mode of action of the contagium. In the first place, granting that during the period of incubation the contagium is being reproduced, and that the termination of that period marks the time at which its reproduction has reached a point at which disturbance of the economy must ensue; and granting further, that the febrile symptoms result from the growth of the contagium particles in the system—granting all this, it is evident that the larger the number of contagium particles which gain entrance to the system, the shorter is likely to be the period of incubation. That period represents the time which is required for the reproduction of the quantity of contagium requisite to produce disturbance of the economy. Suppose a million to be the number of contagium particles required for that purpose, it is evident that that number will sooner be produced from twenty germs than it could possibly be from only one. Supposing that each germ produces four others, it is quite apparent that, starting with twenty, the requisite million will be got sooner than if we start with only one. Now in the natural variola it is doubtful if more than one contagium particle is originally taken into the system; sometimes there may be more, but probably not often. In inoculated variola, on the other hand, it is certain that very many are introduced. The exact number it is impossible to determine, but from what we know of the relation which the small-pox poison bears to the matter of its pustules, it is probable that the quantity of matter used for inoculation would contain not less than twenty or thirty, it might be even two or three hundred, contagium particles.

In the larger number of germs which gain entrance to the system we have an adequate explanation of the fact that inoculated variola has a shorter period of incubation than the natural disease.

This is an agency which, it is evident, may operate in any of the specific fevers. The variation in the duration of the period of incubation which is noted in connection with each of them may thus be, to some extent, explained by the variation in the number of germs received.

In the case of variola there is another agency which may aid in shortening the period of incubation of the inoculated disease. Contact with its second factor is necessary to the propagation of the contagium. In small-pox this second factor has its seat in the skin; such being the case, it is evident that contact of the two factors, and, therefore, the symptoms to which the propagation of the contagium gives rise, may be more speedily brought about when the first factor is introduced directly into the cuticular circulation, than when it reaches it indirectly through the lungs and general circulation. In the former case, it is brought into immediate contact with its second factor, and at once begins to be propagated; in the latter, it may circulate in the blood for some time before it enters a cuticular vessel. On this view of the matter, the period of incubation of inoculated variola *ought* to be shorter than that of the natural disease.

There is another interesting fact in the history of variola which it may seem difficult to explain in any way, but of which this hypothesis also affords a feasible explanation. Inoculated variola is generally milder than the natural disease. On no view hitherto advanced can that be explained; on that now advanced, we think it may. It has just been said (and, though incapable of proof, the fact is so obvious that no one will be disposed to deny the possibility of the occurrence) that a contagium particle may enter the circulation through the lungs, and may circulate in the blood for some time without coming in contact with its second factor. It is evident that the larger the quantity of the second factor, the less the chance of such an

occurrence. The larger the quantity of the second factor in the system, the more violent also is the attack. Those whose systems contain much of the second factor are thus more susceptible, and more apt to suffer severely when seized, than those whose systems contain less of it. Each is equally likely to inhale the contagium, but in the latter there is a greater chance of its again passing out, without coming in contact with its second factor. There can be little doubt that such an occurrence does sometimes take place, and that the small-pox poison enters, circulates in, and passes out of the system, without reaching its second factor, and, therefore, without doing harm. Those in whom this occurs most readily are those whose systems contain little of the second factor, and who, if they took the disease, would have it mildly.

Such is what obtains in the natural disease. Those who have much of the second factor, and who, when seized, suffer severely, have little chance of escape if the contagium enter their system. Those who have little of the second factor, and who, when seized, suffer much less severely, have a greater chance of escape, in consequence of the increased chance of the contagium passing from their systems without coming in contact with its second factor.

When the poison gains entrance by inoculation there is no such chance. Here there is no selection. All are inoculated without reference to their susceptibility. The contagium is introduced directly, and in larger quantity, into the cuticular circulation, and is thus in every case brought into immediate contact with the seat of its second factor. The chance of escape is thus done away with; all who thus receive the poison, no matter what their natural susceptibility, take the disease—those who have much of the second factor, severely; those who have little of it, mildly. It is obvious that in inoculated variola, in which all alike are seized, the proportion of mild cases must be very much greater than in the natural disease, in which paucity of the second factor so much favours the chance of escaping the disease altogether.

The fact that the natural disease may be as mild as the

inoculated, and that the inoculated may be as severe as the natural, sufficiently shows that inoculation, as such, is not the sole cause of the mildness of cases so induced.

Let us consider now the case of typhoid fever.

Of the common specific fevers this is the least contagious. To so slight an extent is it so, that by many it is not regarded as contagious at all. There are, however, facts sufficient to show that it may thus be communicated; but the paucity of such facts, as compared with the frequency of the disease, sufficiently shows that, in the matter of contagiousness, it differs materially from the other common specific fevers.

We have seen that the degree of contagiousness of a given fever depends (*a*) on the quantity of its contagium which exists in the surrounding atmosphere, and (*b*) on the readiness with which this reaches its second factor through the circulation. The former depends on the seat of the local lesion with reference to the surrounding atmosphere; the latter on the extent of distribution of the second factor.

Typhoid fever is the only one of the common specific fevers in which no direct relation exists between its characteristic local lesion and the surrounding atmosphere. Whatever is given off from its lesion passes, not directly into the atmosphere, but gains exit from the body with the intestinal discharges, and with them is speedily removed from the atmosphere which the patient breathes. So far as the giver of the contagium is concerned, typhoid fever ought, therefore, to be the least contagious of the common fevers; and all experience shows that it is so.

Of the extent of distribution of the second factor we judge by the extent of tissue involved in the local lesion. In typhoid fever the local lesion is confined to narrow limits, the glands scattered over a foot or two of the small intestine. It is only in this limited space that the contagium of typhoid fever finds that second factor, contact with which is essential to its propagation. The difficulty which the contagium experiences in reaching its second factor in so

narrow a compass is one of the chief causes of the slight degree of contagiousness which belongs to this form of fever.

Suppose that a typhoid germ gains entrance to the circulation. It will be sent from the heart along with the general column of blood; it may pass into the carotids, the subclavians, or down the aorta and into the iliac arteries, or into any of the aortic branches except those which lead to the glands specially involved in the disease, without the chance of being propagated, and, therefore, without the chance of doing harm.

Contrast with this what takes place in the case of small-pox, measles, or scarlet fever, and the importance of the extent of distribution of the second factor as an agency in determining the degree of contagiousness of the eruptive fevers will be apparent. In these diseases the germ may pass into the carotids, the subclavians, or down the aorta and into the iliac arteries, in short, into any of the main channels of the circulation, and still reach a cuticular vessel. Only in the visceral arteries does it not have this chance. The quantity of blood which goes into the main arteries forms such a large proportion of the circulating fluid that the chances are much in favour of its containing the contagium.

In typhoid fever, on the other hand, the quantity of blood which goes to the glands involved in the local lesion is such a fractional portion of the general mass of the circulating fluid, that the chances must be very much against its containing the minute particle which constitutes the contagium. There are, too, so many chances in favour of the contagium passing out of the system by the lungs, skin, or other eliminating organ, that it is probable that the majority of typhoid germs which gain entrance to the circulation through the lungs, or otherwise than through the glands specially involved in the disease, are eliminated without ever coming in contact with their second factor, and, therefore, without causing disturbance.

The degree of contagiousness which, according to this view, should theoretically pertain to typhoid fever, corre-

sponds very closely to that which experience shows it to possess.

But the lungs are not the only channel through which the contagium may gain entrance to the system. It may be taken in with the food or drink. The poison of typhoid fever does frequently enter the system through the alimentary canal, especially through the medium of contaminated water; and experience shows that, when thus received, it acts more certainly than when inhaled from the atmosphere. It acts with greater certainty because the contagium reaches its second factor more readily and more certainly by way of the digestive canal than by way of the circulation.

The magnitude of the danger which attends the reception of the poison of typhoid fever into the digestive canal is well illustrated by what occurs when a little of that poison is mingled with milk; a very slight contamination of the milk suffices to produce most serious results. The history of the various outbreaks of the disease which have been traced to this cause shows that contaminated milk is a greater source of danger than the water from which it receives the poison. It is so, first, because milk is used only as an article of diet, and is, therefore, all taken into the alimentary canal; while water is used for many other purposes; and, second, because the germs in the water are more frequently destroyed by boiling than are those in the milk. So marked is the infecting power of contaminated milk, that it has been supposed by some that typhoid germs find in that fluid the pabulum requisite to their propagation, and that to such propagation taking place in the milk is to be ascribed the intensity of its infecting power.[1] Such an hypothesis is quite unnecessary: the two reasons just given being adequate to explain all.

The production of typhoid fever by the reception of the poison into the alimentary canal bears a close resemblance to the production of variola by inoculation. The peculiarity in each case is that the poison is brought into direct con-

[1] *Lancet*, vol. i. 1876, p. 644.

tact with its second factor, and is, therefore, sure to be propagated. In either case the passage of the contagium into the circulation through the lungs involves a chance—in the case of typhoid fever a very great chance—of its passing out through some eliminating organ without coming in contact with its second factor.

But the chemist may say, 'If the seat of the local lesion contain something which is essential to the propagation of the organism, surely we should be able to detect its presence, and demonstrate its existence, in a more certain way than by such pathological evidence as has been advanced.'

To him in reply it may be said: 'Is your science so advanced, and so perfect, that you can detect by its aid the presence of everything which exists in nature? Are there not many substances whose existence you recognise, but whose presence chemical science is unable to demonstrate? Can you, for instance, by all the aids of your science tell me, what I by my unaided senses can tell you—that this is cod, and that is haddock; that this is beef, and that is mutton; that this is grouse, and that is partridge; that this is snipe, and that is woodcock? Or can you tell me what it is that gives to each animal an odour so peculiar that, by the sense of smell alone, one may distinguish a horse from a cow, a dog from a cat, a sheep from a goat, a fox from a badger? Or, more wonderful still, can you tell what it is that enables a dog by its nose to recognise its master, and unerringly to track his course over ground which has been traversed by many other men, the scent of whom it must perceive, but at once distinguishes from that of its master?'

It is a practice among shepherds, when a ewe dies, to get another one which has lost her lamb to suckle the one whose mother is dead. But the foster-mother at once finds out that it is not her own lamb, and refuses to suckle it; and she cannot be got to do so until the skin of her own dead lamb is fixed on the living one. She is deceived by the odour of the skin, and allows the lamb, which she before butted away, to suck her teats. One cannot watch the actions of ewes and lambs during the first few days of the

latters' existence without seeing that it is by the sense of smell that the mother distinguishes her own offspring.

The various instances which have been given of the existence of substances whose presence the chemist cannot demonstrate, suffice to show that his inability to detect the presence of what we have called the second factor in the seat of the local lesions of the specific fevers, cannot be regarded as a valid argument against its existence.

Such an objection on the part of the chemist is more than met by the broad and undeniable fact that each parasite has a special nidus in which alone it is propagated. The nidus necessarily contains something which is essential to the propagation of the parasite, and which does not exist over the body generally. The time may come when the chemist will be able to tell us what this substance is: meantime, his inability to do so cannot overturn the positive evidence of its existence, gained from a study of the natural history of parasitic organisms.

THE DIFFERENT DEGREES OF SEVERITY IN WHICH THE SAME FORM OF FEVER OCCURS IN DIFFERENT PEOPLE.

This is generally referred to individual susceptibility; and an analogy drawn between this, and what is observed in the case of ordinary poisonous and medicinal agencies. But we have seen good reason to believe that the poisons of the eruptive fevers do not act in the same way as ordinary poisons, but that their action is intimately connected with their organic growth.

How it is that some individuals show a peculiar susceptibility or the reverse, to the action of certain ordinary poisons, we do not know; for to refer it to individual susceptibility is to indicate, not to explain, the fact. Nor, indeed, do we know how it is that what we regard as the ordinary and normal action of such agencies is brought about. We know from experience that such and such a drug produces such and such an action on such and such

an organ; that, for instance, digitalis acts on the heart, and cantharides on the bladder; that opium contracts, and belladonna dilates the pupil. But why each produces its own peculiar action, and why digitalis never irritates the bladder, and opium never dilates the pupil, we cannot tell.

Under these circumstances, to bound our knowledge of the mode of action of the poisons of the eruptive fevers by what we know of the mode of action of ordinary poisons, would be wilfully to restrict and curtail it. We do not know how all ordinary poisonous and medicinal agencies produce their peculiar effects; but that is no reason why we should not strive for a more precise knowledge of the mode of action of the poisons of the eruptive fevers. These we have seen to be essentially different in their nature from ordinary poisons. We have seen also good reason for believing that the peculiarity of their nature gives rise to a corresponding peculiarity in their mode of action. The local lesions which characterise their action are most readily explained on the view that the site of these lesions, is also the nidus of the parasite; while the general symptoms to which they give rise bear an intimate relation to their organic growth. What we have now to consider is the question why, with the same dose of the poison, both the intensity of the local lesion, and the severity of the general symptoms, vary so much in different cases.

First, as to the local lesion. The hyperæmia which constitutes this we have seen to be the necessary accompaniment of the propagation of the germs in the nidus. The degree of hyperæmia, and the extent of the action which takes place in the nidus, and consequently the intensity of the local lesion, will depend on the number of germs fecundated. This, in its turn, will depend on the richness of the nidus. In other words, the extent to which the second factor exists in the nidus, is the agency which determines the extent of the propagation of the contagium, and the degree of intensity of the local lesion. If the second factor exist only to a small extent, the action which takes place in

the nidus will be comparatively limited, and the resulting local lesion correspondingly slight. If it exist to a large extent, the action which takes place in the nidus will be proportionally great, and the resulting local lesion correspondingly severe.

The general febrile symptoms result from the growth of the germs in the tissues. The degree of their severity depends on the extent to which the contagium particles are reproduced; that, in its turn, depends on the fecundating powers of the nidus; and thus the same agency which determines the extent of the local lesion, determines also the amount of febrile disturbance by which such lesion is accompanied.

In accordance with this, we find that the severity of the general symptoms bears a direct relation to the prominence of the local lesion. In small-pox and typhus fever the more severe the case the more abundant the eruption. In measles and scarlatina the smartness of the attack is indicated by the quantity of the eruption, or by the severity of the pulmonary and throat symptoms. In typhoid fever the severity of the disease is directly as the extent of the bowel lesion. In cerebro-spinal fever, the danger is directly as the extent of the meningeal mischief.

Here an apparent difficulty presents itself. If such be the nature of the connection which obtains between the local lesion and the general symptoms, how are we to explain the occurrence of those cases in which no local lesion is developed—variola sine variolis; morbilli sine morbillis; typhus sine eruptione?

There are two possible explanations.

It may be that such cases are instances of mistaken diagnosis. There are so many causes capable of giving rise to a febrile attack of short duration, that one of them may very readily act on an individual who has recently been exposed to one of the specific fevers, and in whom, therefore, any febrile symptoms which present themselves, are apt to be traced back to such exposure. The fatigue and anxieties inseparable from attendance on one suffering from fever, may alone suffice in some persons to produce such an attack

A febricula accompanied by gastric irritation in one who has been exposed to the contagion of small-pox, may thus become a variola sine variolis: accompanied by catarrhal symptoms in one who has been exposed to measles, it may be called morbilli sine morbillis: a non-eruptive febrile attack in one resident in a house in which there are cases of typhus, is typhus sine eruptione.

The main ground for the diagnosis in each case is the fact that the patient has been exposed to infection. In many cases, the diagnosis may be wrong; but it probably is not so in all. For there is good reason to believe that the poisons of the eruptive fevers sometimes produce febrile disturbance, without giving rise to the usual local lesion. Next to the absence of the local lesion, the most prominent characteristics of these cases, supposing them to be attacks of eruptive fever, are their mildness, and the shortness of their duration. Now, if it be the case that the quantity of the second factor is the agency which determines both the extent of the local lesion, and the severity of the general symptoms, and if it be true that the amount of the second factor which the system contains varies so much in different individuals, it is evident that in some it may exist to so slight an extent that there may not be sufficient for the production of a characteristic attack of the disease. In the case of typhus, for instance, there may be enough of the second factor to produce just so much febrile disturbance as exists during the first two or three days of an ordinary attack, before the eruption comes out, but not enough to produce a characteristic seizure, and not enough to lead to the amount of local hyperæmia requisite to the development of the rash.

In measles there may be an abundant eruption, and little or no chest affection; or there may be prominent chest symptoms, and little or no eruption. So with scarlatina, there may be a profuse eruption, and very little sore throat; or a virulent sore throat, and little or no eruption. That is to say, that in cases in which there is apt to be a double lesion, one may predominate almost to the exclusion of the other. This shows that the second factor may

be concentrated in one locality. We have already seen that it may exist to a large, or to a slight extent. Under these circumstances, it is evident that a given individual may have in the mucous surface of his respiratory tract, enough of the second factor to enable the contagium of measles to be propagated in quantity sufficient for the production of some febrile disturbance, but not sufficient for the production of serious pulmonary symptoms. The skin of the same individual may contain none of the second factor. An attack of measles in such a person would consist of a febrile attack of a few days' duration, and some catarrhal symptoms. It would be a feverish cold, or morbilli sine morbillis, according to the view which we took as to its origin.

It is a recognised fact, that typhoid fever may exist in so slight a form, that the duration of the febrile symptoms may be no more than ten or twelve days; in such cases the bowel lesion consists only in some fulness and increased redness of the affected glands; there is no ulceration, and, therefore, there are no bowel symptoms. Analogous, and equally mild, cases may occur in all the eruptive fevers. In such instances the second factor exists to an extent which is sufficient for the reproduction of the quantity of contagium necessary to produce slight febrile disturbance, but is not sufficient for the development in the locality in which it exists of an amount of hyperæmia which is perceptible to the naked eye. There is necessarily some increased blood flow through that locality, but not enough for the development of a lesion.

The true nature of such cases is apt to escape recognition; especially if they occur sporadically. In such circumstances they are very likely to be mistaken for some slight non-specific febrile ailment: and in the symptoms presented by the patient there is nothing to guide us in discriminating between these, and very slight attacks of the specific fevers. The duration of the febrile symptoms, and the circumstances under which they occur, are our best means of doing so. But even these are inadequate; and it is probable that many of the anomalous forms of fever which come under

the notice of the physician are really very slight attacks of one or other of the specific fevers.[1]

But there is yet another class of cases in which no eruption is observed; and whose characteristic is the severity of the seizure. We refer to those cases in which the poison of scarlatina acts with such virulence as to lead to the rapid development of typhoid symptoms, to collapse, and death maybe within twenty-four or forty-eight hours of the seizure, without the occurrence of eruption or sore throat.

If the second factor be necessary to the propagation of the contagium, how are these cases to be explained? In the first place it is to be noted that it is not always strictly accurate to say that there is no local lesion: for though there may be no throat symptoms, the fauces are often of a deep red colour—they are hyperæmic. In the second place it is to be observed, that one of the prominent symptoms of such cases is the frequent passage of watery stools. The watery stools and the collapse may even give the patients the appearance of those suffering from cholera. Cases of scarlatina in which diarrhœa occurs are always anxious ones; and such diarrhœa is particularly troublesome. The probable explanation of this symptom is, that the bowel congestion which leads to it, is similar in nature to the throat affection and to the skin eruption. In other words, the second factor in some cases of scarlatina has its seat in the intestinal mucous surface. In such cases diarrhœa is a troublesome symptom. If the second factor exist to a large extent in that locality, this symptom may predominate to the exclusion of the eruption and sore throat; and the patient, though suffering from the action of the

[1] Dr. Tweedie believes that all cases of febricula are mild cases of typhus or relapsing fever. (*Lumleian Lectures*, 1860.)

Murchison regards it as probable that many cases of febricula result from a small dose of the typhus-poison (*op. cit.* p. 187). He also says that most cases of 'simple continued fever,' or 'febricula,' are abortive attacks of enteric fever (*op. cit.* p. 457).

In this view (no doubt the correct one) of the pathology of many cases of febricula, we have the probable explanation of the occurrence of those cases of typhus and typhoid fever, in which the disease is believed to have originated *de novo*.

poison of scarlatina, may die, less with the ordinary symptoms of that disease, than with those of cholera,—diarrhœa, and collapse.

It is evident from all this, that the view which regards the amount of the second factor as the agency which determines the severity or the mildness of a particular seizure, is the one which best explains the facts with which we have to deal. The presence of this second factor in the system it is which constitutes individual susceptibility, and the extent to which it exists it is which determines the degree of such susceptibility.

IMMUNITY FROM SECOND ATTACKS.

Exhaustion of susceptibility to the action of the poisons of the specific fevers is one of the most remarkable features in the natural history of these maladies, and one of the most striking of the results consequent on the action of their poisons.

Of no ordinary organic or inorganic poison can it be said that it acts but once in a lifetime. Habit, indeed, renders the system less susceptible to the action of many of them: but that is quite a different thing from a single dose totally and for ever exhausting the susceptibility of the system to the action of the poison. Such a very remarkable feature in the history of the specific fevers can be explained only on the supposition that, by the action of the contagium, there is produced some peculiar and indelible impression, as a consequence of which the body no longer presents to the contagium all the elements requisite to its propagation.

We have seen that for the production of the specific fevers two factors are necessary; and that the cessation of the febrile symptoms coincides with, and is consequent on, the exhaustion of the second. It is this exhaustion of the second factor which constitutes the permanent impression left by an attack of one of the specific fevers. Of what this second factor consists we do not in any case know. Its existence cannot be demonstrated any more than that of the contagium. We infer its existence from the facts with

which we have to deal; and from the same facts we conclude that, though a constant, it is not an essential constituent of the human organism. We know that it is a constant element because, speaking generally, every one is susceptible to one attack of each of the specific fevers. We know that it is not essential to the wellbeing of the body, because its exhaustion is followed by no other effects than immunity from a second attack.

That the mere reception of the contagium into the system does not suffice to the production of disease, has been thousands of times demonstrated practically in the case of vaccinia and variola. Matter may be taken from a vaccine vesicle, and inserted into the arm of one who has never been vaccinated, with the certain result of producing in him a similar vesicle. Some of the same matter may, at the same time, and in the same way, be inserted into the arm of one on whom the operation had previously been performed with success, with the certainty that there will either be no result at all, or only a modified one.

And so with variola: one who has suffered from the disease may be inoculated with small-pox matter over and over again without experiencing more discomfort than would result from inoculation with the matter of a simple pustule. It cannot be that the matter is not again absorbed; it can only be that the contagium, thus taken into the system, does not find in it the second factor requisite to its propagation.

If the phenomena which follow the reception of the contagium into a susceptible system result from its propagation in that system: and if individual *susceptibility* consist in the possession of what we have called the second factor; individual *insusceptibility* must be due to the absence of that factor.

That the second factor is used up during the course of the febrile attack, and is not again reproduced, is an opinion which we have seen reason to maintain. Exhaustion of susceptibility we, therefore, attribute to exhaustion, and non-reproduction, of the second factor requisite to the propagation of the contagium.

If any two contagia required and appropriated the same

second factor, the action of the one would probably protect against the action of the other. Thus it is, possibly, that vaccination protects against small-pox.

THE CESSATION OF THE FEBRILE SYMPTOMS.

The cessation of the symptoms which constitute a febrile attack, forms as essential a part of the illness as their onset; it, therefore, equally calls for consideration and explanation.

The propagation of the poison in the system is the cause of the febrile disturbance in the specific fevers. So long as the contagium particles are conveyed to, and find in, the nidus the second factor necessary to their propagation, so long do they continue to be reproduced and to grow. While their propagation and growth continue, the local lesion does not diminish in intensity, and the general symptoms show no signs of abatement. But let this second factor be exhausted, as (if not reproduced as speedily as it is used up in the process of fecundation) it inevitably must be in time, and all those actions and changes which depend on the continued propagation and growth of the germs, must come to an end.

That the second factor is exhausted, and is not again reproduced, is rendered probable by the fact that the contagium cannot, as a rule, be propagated in the system more than once. So long as any of the second factor remains, the contagium continues to be propagated: so soon as it is exhausted, its propagation ceases, and the febrile symptoms come speedily to an end. The cessation of the febrile symptoms is, therefore, due to the exhaustion of the second factor.

It is a strong argument in favour of this view of the important part played by the second factor, that the local lesion begins to decline, or altogether disappears, and the febrile symptoms come to an end, while there is still in the system much of the poison which gave rise to them, but which is now powerless for evil to the body in which it exists, though capable of producing disease in those around. The early days of convalescence from the specific fevers are,

indeed, regarded by some as their most infectious period. I do not think there is evidence to prove this: but there is abundant evidence to show that the febrile symptoms cease, and the local lesion shows signs of amendment, some time before the poison which gave rise to them is eliminated from the system; clearly showing that something more than its *presence* in the system is essential to the production of the febrile state, and of the local lesion.

At the moment at which the exhaustion of the second factor is completed, there must be circulating in the blood a number of germs which have not completed their organic growth. These will continue to appropriate the nutrient ingredients of the blood until their growth is completed. And until they cease to grow, the febrile process will not come to an end. It follows from this that the cessation of the febrile symptoms, and the exhaustion of the second factor, are not exactly contemporaneous. Exhaustion of the second factor is contemporaneous with the moment at which the febrile symptoms begin to decline—it is indeed the cause of this declension. But the complete subsidence of the febrile symptoms must necessarily, for the reason given, be subsequent to the complete exhaustion of the second factor. Hence we find that a sudden cessation of the fever is, in these days of accurate thermometry, unknown in the specific fevers, the process of defervescence always occupying twelve, twenty-four, forty-eight, or more hours.

The cause which gives rise to the fever is the propagation of the poison in the system. The cessation of the fever must, therefore, be consequent on the cessation of this action. The propagation of the poison goes on so long as any of the second factor remains: it ceases when that is exhausted. Exhaustion of the second factor is thus the cause of the cessation of the febrile symptoms, and of the decline of the disease.

THE FIXED DURATION OF THE FEBRILE SYMPTOMS.

This is to be explained in the same way.

One of the prominent characteristics of each of the

specific fevers, is the possession of a fixed and definite period of duration. Seeing a patient suffering from any one of them at a given period in its course, we can tell with tolerable certainty not only the past history, but the probable future course and duration of the illness. For example, seeing an ordinary case of typhus fever for the first time on the day on which the eruption has appeared, we can tell that the patient has been ill five days, and that the febrile symptoms will not begin to decline for other eight or nine days—more or less, according to the age of the patient, and the severity of the case. We can tell also the symptoms which presented themselves during the five days which preceded our visit, as well as those which are likely to present themselves during the remaining period of the illness.

In the case of no ordinary organic or inorganic poison, can we thus, without any knowledge of the quantity taken, scan the past, and prognosticate the future of its action. Seeing a man suffering from the symptoms of arsenical poison, for instance, we cannot, from his symptoms alone, and without further evidence that he has taken poison, at once come to a decided conclusion as to their causation. We may have a decided opinion on the point ; but there can be no absolute certainty. Again, having satisfied ourselves that it is arsenical poisoning with which we have to deal, we cannot, in the absence of information as to when, and in what quantity, the poison was taken, tell either how long it has been acting, or for what time it may continue to do so.

The duration of the period of action of the poisons of the specific fevers is, within certain limits, fixed and invariable. That of ordinary poisons is variable and uncertain. The severity of the action of ordinary poisons depends mainly on the dose taken. In the poisons of the specific fevers the dose is immaterial: that which determines the extent of their action is the amount of the second factor. When this is exhausted the febrile symptoms cease. The fact that the duration of these is, in each of the specific fevers, sufficiently fixed and distinctive to form one of its characteristic features, is enough to show that there is a

pretty constant average quantity of the second factor. It is the existence of this average which gives to each of the specific fevers its fixed duration.

The duration of the febrile symptoms represents the time which the contagium requires to exhaust its second factor. For this purpose the poison of typhus fever requires, on an average, from twelve to fourteen days; that of typhoid fever, on an average, from twenty to twenty-two days. Hence the mean duration of these two forms of fever is respectively two, and three weeks.

RELAPSING FEVER.

The distinctive features of each of the specific fevers which has a local lesion are those derived from this lesion, and the existence of such a lesion is a consequence of the localization of the nidus in some particular structure.

Did there exist a specific fever in which the second factor existed in the blood, and was not localized in any particular organ or structure, the distinctive feature of that fever would be, not a local lesion, but the course of the febrile symptoms. Such a fever is relapsing fever.

The mode of production of the general febrile disturbance in relapsing fever is the same as in the eruptive fevers.

But though possessing much in common with the eruptive fevers, relapsing fever is separated from them by some very prominent points of distinction, which render it necessary for us to consider this form of fever by itself.

The peculiarities by which relapsing fever is distinguished from the eruptive fevers are as follows :—

1. It possesses no characteristic local lesion.
2. During the fever a foreign organism is found in the blood.
3. The course of the febrile symptoms forms the distinctive feature of the disease.
4. One attack confers no immunity from a second.

Let us consider these peculiarities separately and in the order enumerated.

1. *The Absence of a local Lesion.*

The distinctive feature of the eruptive fevers—the possession of a characteristic local lesion—is due to the fact that the nidus in which the contagium finds the material necessary to its propagation, is limited to a particular organ, or part, of the body. The absence of such a characteristic in relapsing fever must be attributable to the absence of that which gives rise to it in the eruptive fevers. The want of a characteristic local lesion in relapsing fever we, therefore, attribute to the circumstance that the second factor requisite to the propagation of its contagium is not localized, but is generally distributed in the blood.

2. *The Presence of an Organism in the Blood.*

In 1868 Obermeier[1] discovered that the blood of those suffering from relapsing fever often contained a foreign organism presenting to the eye the appearance of minute spiral fibres.

Subsequent observations have established, first, that these organisms are never absent from the blood during the period of fever; and second, that they very speedily disappear after defervescence. They are present during the pyrexia, and absent during the apyrexia. Such are the facts. What is their interpretation? What is the relation of the organism to the fever? That it is not accidental is certain. The organism causes the fever; or the fever gives rise to the organism.

(*a*) The view that the fever causes the organism, is that advocated by the opponents of the germ theory. The main argument adduced in favour of this view is 'that the form taken by many minute growths depends not upon the germ, but upon the nature of the medium in which it grows.'[2] And it is presumed with reference to the spirilla of relapsing fever, 'that the soil is suitable for their development during

[1] *Centralblatt*, 1873, No. 10.
[2] Murchison in *Transactions of Pathological Society of London*, 1875.

the febrile process, and unsuitable when the febrile process is completed.'[1] But if the febrile process induce a state of the blood, which favours the development of these organisms, why are they not found in other forms of fever? There are many maladies during whose course the febrile state is as marked as during relapsing fever, but in not one of them has the spirillum ever been found.

Then again, on this view of the matter, how are we to explain the alternation of periods of pyrexia and apyrexia? And if this were explained, how are we to account for the cessation of such alternations, and the permanent restoration of health? That the soil is suitable for the development of the spirillum during the pyrexia, and not during the apyrexia, is evident: but to state a fact is not to explain it. The question is why is it at one time suitable and at another unsuitable?

There is no real evidence to support the opinion that the fever causes the organism. We, therefore, regard it as inadequate to explain the phenomena with which we have to deal.

(*b*) In support of the opposite, and alternative opinion, that the organism causes the fever, various arguments may be adduced.

1. Independently of the presence of an organism in the blood, there is very strong evidence that the poison of relapsing fever, like those of the eruptive fevers, is an organism.
2. The growth in the system of millions of organisms, is competent to produce the phenomena of the febrile state.
3. A peculiar and distinctive organism is invariably found in the blood during the pyrexial stage of relapsing fever.

'That a parasite so clearly determined as this, abounding in relapsing fever, and never having been found thus far in any other disease, must be closely connected with the

[1] Murchison in *Transactions of Pathological Society of London*, 1875.

development and spread of the affection in question, is hardly to be doubted' (Lebert).

When considering the eruptive fevers we found reason to believe (*a*) that the organisms which gave rise to them were propagated in the seat of the local lesions; and (*b*) that they were propagated in that locality because it was there that, as parasites, the contagium particles found the second factor essential to their reproduction; (*c*) that the poisons of these diseases were most abundant in the seat of their local lesions; and we came to the conclusion (*d*) that the organisms were the cause of the morbid process.

In relapsing fever we find no such morbid process, no such localization of the second factor, and no localized growth of organisms. But we find the same evidence of the introduction of an organism from without, as we found in the eruptive fevers; we find too the same evidence of its propagation in the system; and with this, we find an organism abundantly present in the blood. The conclusion is inevitable that the organism is thus distributed in the circulating fluid, because the second factor essential to its propagation as a parasite exists in the blood, and is not, as in the eruptive fevers, confined to a particular tissue.

3. *The Course of the Febrile Symptoms forms the Distinctive Feature of the Disease.*

The characteristic feature of relapsing fever is the relapse. There is a febrile attack of six or seven days' duration; then a period of freedom from fever of a week's duration; then another febrile attack of shorter duration than the first; and then another period of freedom from fever, which is generally permanent: but there may be as many as four or five relapses.

During each period of pyrexia, the spirillum is found in the blood; during each period of apyrexia, it is absent. The pyrexia we have attributed to the propagation and growth of the organism; the apyrexia we must attribute to its absence. And if we can explain the cessation of its pro-

pagation, and the coincident decline of the fever, we shall have accounted for the distinctive course of relapsing fever.

The absence of the spirillum during the apyrexia may be due either to some peculiarity of the contagium, or to some peculiarity of the second factor. If the contagium were an organism which naturally went through a series of changes involving alternate periods of activity and repose; and if the phenomena of the febrile state were the result of such changes as occurred only during the period of activity, it is evident that the propagation of such an organism in the system, would give rise to a malady characterised by alternations of pyrexia and apyrexia. The spirillum might thus give rise to relapsing fever. But if such were the case—if each febrile attack corresponded to the advent of another period of active growth of the parasite, we should probably find some change in its external appearance, some evidence of a further development of the organism. We should probably find, too, that it was present to some extent during the apyrexia. But such is not the case. The spirillum is found only during the pyrexia ; and presents in the second, third, and fourth seizures, exactly the same appearance which it presented in the first.

Again, if such were the explanation of the distinctive course of relapsing fever, we should almost certainly find the course of the malady the same in each case. If the contagium had certain normal stages of development to go through, these stages would always be the same ; and the course of the symptoms to which they gave rise would be the same also. But such is not the case. The number of pyrexial attacks is generally two ; but there may be only one ; or there may be three, four, five, or even six.

For these reasons we conclude that the cause which gives rise to the distinctive features of relapsing fever, is not to be found solely in some peculiarity of its contagium. The only other possible cause is some peculiarity of its second factor.

The peculiarity of the second factor of relapsing fever is its general distribution in the circulating fluid. Could such a peculiarity induce the phenomenon now before us—a re-accession of fever ?

In the eruptive fevers we attributed the decline of the febrile symptoms to exhaustion of the second factor: in relapsing fever we attribute their decline to the same cause.

The permanent duration of convalescence in the eruptive fevers, we attributed to the fact that this exhaustion is permanent—that the second factor is not reproduced: the absence of such permanency in relapsing fever, we attribute to the opposite cause—the second factor *is* reproduced.

The occurrence of the characteristic second seizure of relapsing fever indicates that the second factor is reproduced in the blood before the first is thoroughly eliminated from it: its early reproduction leading to the renewed development of such germs as remain, and a consequent second pyrexial attack. If such be the explanation of the relapse, it is evident that cases might occur in which, either from more rapid elimination of the first factor, or from more tardy reproduction of the second, the first might be thoroughly eliminated before the second was reproduced: the consequence would be the absence of the usual characteristic of the disease—there would be no relapse; the attack being completed by one seizure.

That such cases do occur is an established fact in the history of relapsing fever. Of 2,425 cases which occurred in 1843, and which have been collected by Murchison,[1] 724 had no relapse. Of 100 consecutive cases under Murchison's own care in 1869, four were completed by one pyrexial attack. Of 400 recorded by Litten,[2] six had no relapse.

Again, if the second factor be so frequently and so quickly renewed, it is evident that the process might be repeated more than once, and that a third seizure might be caused in the same way as the second, and a fourth in the same way as the third: the sole requisite to the production of a pyrexial attack, being the reproduction of the second factor prior to the complete elimination of the first.

Such cases are observed in every epidemic. Of 1,500

[1] *Op. cit.* 2nd edition, p. 379.

[2] Quoted by Burdon-Sanderson, *Report of Medical Officer of Privy Council*, New Series, No. iii. p. 42.

cases collected by Murchison a second relapse, i.e. a third pyrexial attack, occurred in 109, or in 1 out of 14; a third relapse in 9, or in 1 out of 166; and a fourth relapse in one of the 1,500. Of Litten's 400 cases $35\frac{1}{2}$ p. ct. had a second relapse (a third attack), while 7 of them had 3, and 3 had 4 relapses.

The mode of production of each seizure is the same: the second factor is reproduced before the first is eliminated.

The course of events in a case of relapsing fever is as follows:—a germ is received into the system, and finding its second factor in the blood, immediately begins to grow and be reproduced there: in time a sufficient number is produced to cause pyrexia; in the course of six or seven days the rapid development of the organism leads to exhaustion of the second factor: in consequence of such exhaustion the contagium ceases to be reproduced, and there is a rapid decline of the fever. But the mass of contagium existing in the blood cannot at once, and suddenly, be eliminated. Some days must elapse before the process is completed. But before the expiry of this time the second factor is reproduced, and the conditions essential to a pyrexial attack again present themselves.

It is probable that the second factor is not absent from the blood for more than a few days, and that the greater part of the interval between the first and second seizures is to be regarded as the period of incubation of the second.

But the question arises, Why do the alternations of pyrexia and apyrexia come to an end? Why should there be only two or three seizures, and not ten or twelve? The probable explanation of this is, that the exhaustion of the second factor during a pyrexial attack is so complete that it cannot at once be replaced, and that the oftener this exhaustion is repeated the more tardy the action by which it is reproduced.

In other words, after having been only once used up, the second factor is more readily reproduced than after it has been exhausted two or three times: the readiness with which it is re-formed diminishing with each successive seizure, till a time is reached at which its reproduction is so delayed

that the whole of the contagium is eliminated from the system before the second factor reappears in the circulation. The advent of this period ushers in permanent convalescence.

In accordance with this view we find that, as a rule, each successive attack is shorter and milder than the preceding one. It is so, because after each successive attack there is reproduced less and less of the second factor. In Litten's cases the mean duration of the

1st attack was	6·6 days
2nd ,, ...	4·9 ,,
3rd ,, ...	3·1 ,,
4th ,, ...	3·1 ,,
5th ,, ...	2·3 ,,

4. *One Attack confers no Immunity from a second.*

The renewed susceptibility to the action of the poison of relapsing fever, manifested by those who have already suffered from the disease, is to be explained in the same way as the relapse. Both are due to the fact that the exhaustion of the second factor is only temporary.

We have seen that in the eruptive fevers, in which one attack confers, as a rule, permanent immunity, the second factor is localised in some particular organ or tissue; while in relapsing fever it is some ingredient of the blood. Now it is evident that a permanent impression is likely to be more readily produced on a formed and stable organ than on a constantly changing fluid like the blood. A contagium which finds its second factor in a localised organ or tissue is, therefore, more likely to produce a permanent impression than one which finds its second factor in the circulating fluid.

Moreover, it is to be noted that some of the tissues which are the seat of lesions in the eruptive fevers are apt to undergo permanent change in the ordinary course of nature—they are, in early life, the seat of actions and peculiarities which are normally and naturally lost as adult life and old age are reached. I would specially instance the tonsils, which are involved in scarlatina; and the intestinal

glands, whose affection forms the characteristic lesion of typhoid fever. The tonsils are in early life the seat of an activity, and of a tendency to inflammatory enlargement, which diminish as adult life is reached, and are altogether lost with the attainment of more mature years. The question of the exact function of these glands is one which we need not stay to consider. It is sufficient for our present purpose to note the fact that in early life (from two or three years of age up to fifteen or sixteen) these glands are more active, and more liable to inflammatory enlargement, than at any subsequent period. This period of activity of the tonsils corresponds to the period of greatest susceptibility to the action of the poison of scarlatina. The system is then most susceptible to the action of that poison, for one reason at least, because the particular organ which contains the second factor essential to the propagation of the contagium is then in its state of greatest activity and perfection. As this activity declines, it is probable that the second factor diminishes in quantity, and ultimately disappears. In this way there may be brought about a natural insusceptibility to the action of the poison of scarlatina, similar to that which results from an attack of the disease.

In keeping with this view of the matter we find that adults who are not protected by a prior attack are often freely exposed to scarlatina without contracting the disease; while young people, similarly unprotected, and much less exposed, very readily take it. The immunity enjoyed by mothers of families, physicians, and nurses, is often attributable to their having already suffered from the disease; but by no means always. All physicians must be familiar with cases, either in their own persons or in others, in which adults who have never had scarlatina have been much and frequently exposed to that disease without suffering from it. Such immunity is almost unknown in children. Those of mature years enjoy a natural immunity from the disease, identical with that enjoyed by children who have already suffered from it: in neither does the system contain the second factor requisite to the propagation of the contagium; in the one, the second factor is lost in the ordinary course of

nature; in the other, it is exhausted by the contagium, and is not again reproduced.

The same mode of reasoning applies to typhoid fever. The glands specially involved in that disease are not equally prominent and active all through life: their period of greatest activity is from ten to thirty years of age, more or less; and that corresponds exactly to the period of greatest susceptibility to the action of the poison of typhoid fever. In infancy these glands are indistinct; but they gradually become more developed after birth, and by the age of two or three years are quite perceptible. From that time they increase in size, and presumably in functional activity, and at the end of the first decade of existence are prominent objects in the walls of the ileum. They continue to increase in prominence, and by the end of the second decade have reached their full size. During the third decade they remain stationary. During the fourth they show signs of diminishing in size, and, therefore, probably in functional activity. They continue to decrease as life advances, and by the end of the sixth decade are so reduced in size and importance that it is probable that their period of functional activity has ceased. The periods of insignificance, of importance, and of subsequent decline, noted in the development and history of these glands, correspond exactly to the periods of greater and less susceptibility to the action of the poison of typhoid fever. In infancy, during which these glands are practically non-existent, typhoid fever is unknown. After two or three years have passed, and when the glands begin to come into notice, the liability to the occurrence of the disease begins to manifest itself, but in so slight a form that it is apt to escape recognition. Only indeed since 1848, when West demonstrated the identity of the two maladies, has the old *febris infantum remittens* been recognised as a mild form of typhoid fever. By the end of the first decade the susceptibility to the action of the poison is pronounced; it increases during the second; reaches its height towards the end of it; remains pretty stationary during the third; declines during the fourth; and continues to decline till, at the end of the sixth decade, the suscepti-

bility to the disease is so slight that it may be regarded as practically worn out.

Finding the liability to the occurrence of typhoid fever correspond so closely and so intimately to the period of activity of the glands whose lesion forms the characteristic feature of the malady, we cannot avoid the inference that the presence of these glands, or of something which they contain, is essential to the action of the poison of that disease.

Regarding that poison as a parasitic organism, which is propagated in the system during the course of the malady to which it gives rise, and whose action is intimately connected with its organic development, it seems to me that the view which regards the intestinal glands as the nidus in which the parasite finds the second factor necessary to its propagation is the one which affords the best and most satisfactory explanation of the occurrence of the phenomena with which we have to deal.

The same insusceptibility to the action of the poison of typhoid fever, which is naturally and slowly developed as years advance, may be artificially and rapidly induced by the destruction of the intestinal glands during an attack of that disease.

What has been said regarding scarlet and typhoid fevers, and the mode of production of their local lesions, serves to illustrate the manner in which localisation of the second factor may lead to permanent immunity from the disease.

It serves also to show how the absence of such localisation of the second factor may, in relapsing fever, be the cause of the absence of immunity from a second attack which characterises that disease.

TREATMENT.

Though the immediate object of every theory of fever is to elucidate the natural history of febrile ailments, and to give a reasonable explanation of their phenomena, its ultimate end is to afford a basis for a rational system of treatment. This test of practical utility is the crucial one by which every theory must be tried, and on the results of which its final acceptance or rejection must depend.

The modern treatment of fever is founded not on any theory as to its mode of production, but solely on the results of clinical experience. These results have abundantly demonstrated that there is no form of treatment applicable to all forms of fever. That which has been found to be a specific in intermittent fever is of no avail in the continued fevers: that which arrests rheumatic fever is without influence in pneumonic fever. The broad result is that there are some fevers which can be cut short; others which cannot. The question as to why this is—why quinine cures intermittent, and salicin cures rheumatic fever, and why neither has a like curative effect in any other fever—is one that has to be considered in dealing with the general question of the causation of different febrile states. No theory of fever can be regarded as adequate, or as fulfilling the required conditions of a satisfactory theory, which does not explain why it is that a remedy which arrests the course of one form of fever has no influence on that of another.

The question, being a purely clinical one, must be considered from a clinical standpoint. The subject will be most conveniently approached, and the theoretical fitness as well as the practical application of each form of treatment

best demonstrated, by considering separately those forms of fever in which experience has demonstrated the beneficial effects of a particular line of treatment. We shall, therefore, consider it under the following heads:—

1. The treatment of the specific fevers.
2. The treatment of malarial fevers.
3. The treatment of rheumatic fever.
4. The action of febrifuge remedies.

1. *The Treatment of the Specific Fevers.*

The cause of these fevers, and of all the phenomena which go to constitute them, is the propagation in the system of minute organisms.

The action of these organisms may be met, and the course of the fever arrested or modified, in one of three ways:—

(*a*) By the destruction of the organism.

(*b*) By rendering the system insusceptible to its action.

(*c*) Failing these two, by guiding the patient through his illness, and preventing the poisons from producing fatal effects.

(*a*) The first way is ideally the best, and is conceivably attainable. Though we do not at present know of any agencies capable of destroying in the system the poisons of the specific fevers, it is quite possible that such agencies may yet be discovered. One of the practical results of the study of the natural history of minute organisms has been the recognition of the existence of agencies which exercise a destructive action on these organisms; and a new group of remedies has been suggested and given a local status as therapeutic agents under the name of 'germicides.' Our acquaintance with these agencies is at present very limited; but it may reasonably be hoped that as our knowledge of individual germs and their conditions of life increases, so also may our knowledge of the means of destroying them.

There are some, and there may be many germicides which, while fatal to germs, are not injurious to the human body. If we could find one which was fatal to the germ of typhoid fever, but which could be taken with impunity by

man, that germicide would arrest the course of typhoid fever. And so with all the specific fevers—the germs of each are destructible; and it is well within the range of possibility that agencies may yet be discovered by which their destruction may be effected in the system, and their morbific action thus arrested. All this is possible; and in the possibilities thus opened up we have a wide and hopeful field of research. The recognition of the existence of such agencies as germicides, and the possibility of dealing with diseased processes, and actually curing disease, by means of agencies which do not necessarily have any action on the system—which act directly not on the sufferer, but on that which makes him suffer—the recognition of such a possibility marks an epoch in therapeutics, and opens up a vast and interesting field of research.

So far as the specific fevers are concerned, no advance has been made in this direction. We know of no agency capable of destroying the poison of any one of them, or of arresting the course of the malady to which it gives rise. The subject, therefore, cannot at present be usefully pursued any further.

(*b*) The rendering the system insusceptible to the action of the germ would be not less effective than destruction of the germ in preventing its morbific effects. That the system may be rendered insusceptible to the action of such poisons as these of the specific fevers is an established fact in the history of such ailments; for, as a rule, one attack confers immunity from a second. If the immunity, the insusceptibility to the action of the poisons of the specific fevers which is thus acquired, could be induced artificially by other and safer means, there could by such means be established a general immunity against the action of the poisons of these fevers which would enormously diminish their prevalence, and might in time lead to their extirpation. This is not mere empty speculation, for the thing has already been done in the case of one of them—viz. small-pox. Efficient vaccination prevents small-pox by rendering the system insusceptible to the action of the small-pox poison. If we could find among the lower animals a

disease which bore to measles the same relation that vaccinia does to small-pox, the induction of that disease in man would probably render him insusceptible to the action of the measles-poison. In all the specific fevers we might thus be able to induce such modified attacks as would establish immunity without causing serious illness.[1] In the whole range of practical medicine there is no more promising field of inquiry than this—none which holds out greater potentialities—none whose successful pursuit could more effectually tend to lessen the ravages of disease and save human lives. But it is a treatment which is preventive rather than curative, and could not come into play after the fever had commenced. Vaccination prevents small-pox, but is of no use in the treatment of that disease. As a means of treating the specific fevers this plan of rendering the system insusceptible to the action of their poisons, therefore, is not applicable, and does not come within the scope of our present inquiry.

(*c*) To guide the patient through the disease is thus the plan of treatment to which we are for the present limited. Given a case of any one of the specific fevers, what we have to do is to keep the patient alive till the disease has run its course. In applying ourselves to this task we must bear in mind that the morbid condition with which we have to deal is essentially one in which the tissues are being starved—in which the brain, the heart, the lungs, the liver, the kidneys, the muscles, and all the organs of the body are being deprived of the material requisite to their nutrition and repair. It is evident that symptoms so produced must be adynamic in nature, and that the treatment of such a condition must essentially consist in supplying, so far as we can, the ma-

[1] When we come to know more about the diseases of our domestic animals we shall be in a better position to consider the possible relation of these diseases to those from which man suffers. The catarrhal symptoms of measles bear a resemblance to the catarrh from which cats are known to suffer; the mousy odour of a typhus patient would suggest the possibility of that disease being allied to some disease of the common house mouse. There is in this no improbability which, but for Jenner's demonstration, would not equally apply to the cases of small-pox and vaccinia. There is in it a possibility which should make us pause before accepting the octrine of the *de novo* origin of infectious diseases.

terials of which the tissues are being deprived by the action of the contagium. The action of the contagium essentially consists in the consumption of nitrogen and water destined for the tissues: both tissues and contagium are consuming nitrogen and water: but the system contains no more than is requisite for the tissues alone: the contagium helps itself from this store, and the amount taken up by it represents a direct loss to the tissues. As we cannot prevent this action of the contagium, the only way in which the loss can be made up for, is by throwing nitrogen and water into the system. That is the treatment which is theoretically appropriate to the condition with which we have to deal. It is also the treatment which practical experience has shown to be the most successful. Clinical evidence abundantly testifies to the fact that, in the treatment of the specific fevers, everything is secondary to the administration of water and easily-digested food, to good ventilation, and to the procuring of sleep. This drug may be lauded, that found useful, and a third be supposed to mitigate the severity or curtail the duration of the febrile symptoms; but all medication is confessedly secondary in importance to the regular administration of milk and beeftea, an abundant supply of water, an ample supply of fresh air, and the avoidance of all that is calculated to cause fatigue and excitement. By careful observation of its accompanying phenomena we have learned that when death ensues in fever it is brought about by failure of the heart's action, or by failure of cerebral function; and the treatment which experience has dictated is that which tends to nourish the heart and brain, and keep them up to their work. Malnutrition of these organs, consequent partly on increased disintegration, partly on the consumption by the contagium particles of the nitrogen and water requisite for the renewal of their rapidly wasting tissues, is the cause of the symptoms which present themselves to our notice. Such malnutrition and abnormal metabolism are the essential conditions which have to be dealt with in treatment. The administration of milk, beeftea, and water has the effect of remedying so far as we can the injury thus done to the tissues. Such

administration simply means supplying them with nitrogen and water, the elements required for their nutrition and repair. Good ventilation means a proper supply of oxygen, whose consumption is necessarily increased by any process which causes increased consumption of nitrogen and water. The avoidance of excitement, and the procuring of sleep, simply mean the avoidance of wear and tear, and the husbanding of the nervous energy requisite for the continuance of the processes of life. To this position, and to the adoption of this method of treatment, we have been led by clinical experience, uninfluenced by any theory as to the mode of production of fever. It has been found from practical experience that to feed the patient, and to keep up his strength, is the mode of treatment which gives the best results. It is a clinical fact that such is the case. And it is an additional argument in favour of the metabolic theory of fever, and of the germ theory of its mode of production, that they afford a sound pathological basis for that mode of treatment which clinical experience has shown to be the most successful.

The extent to which the system suffers in a given case of fever depends on the severity of the attack: that in its turn depends, *cæteris paribus*, on the amount of the contagium reproduced in the system. In mild cases that is not great, the fever does not run high, the symptoms are comparatively slight, and the patient gets well under almost any treatment. In moderately severe cases more care is requisite, nourishment may have to be given more frequently, some stimulant may be advisable towards the end of the attack, especially in weak or elderly patients, and it may be necessary to give something to procure sleep. In severe cases the failure of cerebral and cardiac power is more urgently a source of danger; and much care and skill may be requisite to guide the patient through the dangers by which he is beset. The watchful care of a skilful physician, and the active co-operation of an intelligent nurse, the judicious use of stimulants, or a well-timed sedative, the timely use of cold, may enable the patient to weather difficulties and dangers which, without such aid, could not

be surmounted; may turn a wavering balance in the patient's favour, and save lives which would otherwise be lost.

2. *The Treatment of Malarial Fevers.*

A proper and scientific consideration of this question presupposes some idea of the nature and mode of action of the malarial poison.

The opinion most generally entertained nowadays is that the malarial poison consists of minute organisms. 'I have no hesitation,' says Niemeyer, 'in saying decidedly that marsh miasm—malaria—must consist of low vegetable organisms.' Though the evidence is scarcely sufficient to warrant so strong a statement, there can be no doubt that this is the view which best accords with the phenomena noted in connection with the origin and spread of malarial disease; while the researches of Lanzi and Terrigi, and of Klebs and Tommasi-Crudeli, point to the conclusion that the malarial poison is an organism which may be obtained from the soil, and may even be cultivated in the bodies of animals. Still more recently the observations of Crudeli have been repeated and confirmed by Dr. Schiavazzi of Pola, and Professor Cohn of Breslau.

The balance of evidence and of authority undoubtedly favours the view that malarial poisons are minute organisms. If such be their nature, they are more likely in their mode of action to resemble contagia than ordinary medicinal agencies, their specific effects being associated with their organic development.

Of all diseases intermittent fever is that in which the power of medicine to control a morbid process is most marked. By the administration of quinine in sufficient quantity the course of that fever can be arrested, and by its continued administration the recurrence of the malady prevented. The question before us, therefore, resolves itself into consideration of the manner in which quinine produces its curative effects. Quinine cures ague. That is one of the best-established facts in practical medicine. How does it do it? That is the practical question with which we have

to deal. It is not, as in the specific fevers, a question of merely guiding the patient through the fever. That plan of treatment may, therefore, be left out of consideration. Here he is cured at once, and the natural course of the disease arrested. This result is produced in one of two ways—either the quinine so acts on the system as to render it proof against the action of the malarial poison, or it so acts on the malarial poison as to deprive it of its power of affecting the system. The action is on the system, or on the poison; which is it? Those who uphold an exclusively neurotic theory of fever would naturally regard the action as being on the system, and the curative effects of quinine in malarial fever as attributable to its power of inhibiting heat production.

Given in large doses, ten to thirty grains, quinine possesses the power of lowering the temperature of the body when unduly elevated. Is its curative action in malarial fever due to this, or to some other and special remedial action?

In virtue of its febrifuge properties quinine has been given in all febrile ailments; and it was at one time claimed for it that it possessed the power of cutting short typhus. More recently it has also been claimed for it, as for other febrifuge remedies, that it exercises a distinctly curative action in typhoid fever and shortens the duration of that malady. But this conclusion is not supported by adequate evidence. The point is one which could readily be proved, and would long ago have been proved had the facts been as some have stated them to be. I have given quinine largely both in typhus and in typhoid fevers. My experience entirely accords with that of Murchison, who says, with reference to both typhus and typhoid fevers, that he had 'seen no evidence that, at whatever stage it was given, it shortened the course of the disease or diminished its danger.'[1] That large doses do produce a temporary lowering of the temperature is certain, but the effect is very transient, seldom lasting for more than a few hours. Though the temperature is lowered by quinine, the morbid

[1] *On Continued Fevers*, 2nd edit. p. 283.

process which constitutes the disease still goes on: in a few hours the antipyretic action of the drug passes off, and the disease runs its course uninfluenced by what has taken place.

In intermittent fever its action is quite different. Here the quinine actually cures the fever. It not only lowers the temperature but puts a stop to the whole morbid process, and to all that constitutes the disease; and it does this so constantly and so certainly, and its beneficial effects are so lasting, that its action cannot but be regarded as peculiar, and as differing in kind from that action by which it produces a mere temporary lowering of the body heat in other febrile ailments.

That the curative action of quinine in intermittent fever is not to be explained solely by its general febrifuge properties—by its general power of lowering febrile temperature—is evidenced by the fact that it has the power of preventing such fever. Given during the intermission it prevents the fever from coming on. It exercises a distinctly prophylactic action; and when taken regularly and in sufficient quantity by those living in malarial districts, prevents them from suffering as they would otherwise do. It has no such action in any other febrile ailment.

Besides its febrifuge property (the nature of which will be considered later) quinine has no other action on the system by which its curative effects in ague can be explained. This property is not enough to explain its remarkable power of arresting the course and guarding against the occurrence of that disease. We are thus forced to the conclusion that this effect is not to be explained by any action which that drug possesses on the system.

The alternative view is that it acts on the poison of intermittent fever and deprives it of its morbific properties. Granting this poison to be an organism which is reproduced in the system, and whose morbific action is associated with its organic development, there are two ways in which quinine might prevent it from exercising its usual action. It might supply to the poison the material requisite to its development, and so prevent it from taking this from the system: or it might simply destroy the poison.

In support of the first suggestion it is difficult to find anything to say except that it is not impossible. But as the materials requisite for the growth and propagation of an organism are mainly nitrogen and water, it is evident that quinine is not to be regarded as a source whence these are likely to be got. This, therefore, cannot be regarded as the mode in which its curative effects are produced. There remains the alternative view that quinine acts by destroying the malarial poison, and that it is not as a febrifuge, but as a germicide, that it cures ague.

When considering the question of the treatment of the specific fevers, it was stated that the ideal method of treatment was the destruction of the organism which produced the disease, by an agency which had no deleterious effect on the system; and a reference was made to the possibility of thus curing disease by agencies which owed their good effects not to their curative action on the system of the sufferer, but to their destructive action on that which made him suffer.

The ideal is the same in intermittent fever; only here the ideal seems to have been attained. Regarding the poison of that disease as a minute organism, there is nothing improbable in the view that quinine should exercise a destructive action on it, for we know, from the investigations of Binz, that quinine possesses in a remarkable manner the power of destroying many minute organisms. It thus accords both with what we believe regarding the ague poison, and with what we know regarding the action of quinine, that this drug might possess the power to destroy that poison. A careful consideration of all its possible modes of action has driven us to the conclusion that this is the only one that adequately explains the effects which we find it produce in ague. We, therefore, hold that quinine cures ague by destroying the ague poison, and not by any action on the system. It is scarcely necessary to point out that such an action would quite explain its prophylactic as well as its curative effects.

But, it may be said, if quinine owes its curative action in intermittent fever to its germicide properties, why is

this action not manifested in other fevers equally due to the propagation of minute organisms in the system? There are many other febrile ailments produced in the same way. Why does quinine not cure these too? The answer is very simple. In the natural history of minute organisms the fact has been established that different organisms are possessed of specific differences, of whose existence their external form gives no evidence. One flourishes under conditions which are fatal to another; different media are required for the cultivation of different organisms; and it is often only by the medium in which it grows that the true nature of an organism can be defined. Again, the action of colouring reagents on them is different; and such reagents are the only means by which the presence of some organisms can be demonstrated. Organisms possessed of specific differences might have these differences manifested, not only by the different effects which they produce on the system, but by the different effects which other agencies have on them. The fact that quinine does not destroy the poisons of typhoid fever, diphtheria, measles, scarlet fever, &c., is no argument against the view that it owes its curative effects in ague to a destructive action on the poison of that disease. That it is possessed of germicide properties has been abundantly demonstrated. That it is in virtue of its action as a germicide that it cures ague is the belief to which we have been led by a careful consideration of all the facts of the case.

In this view we have a hopeful indication that other agencies may yet be discovered capable of exercising a like effect in other diseases which we are at present powerless to control. But in such an inquiry there must be steadily kept before us the probability that, just as each germ has its own special life-history, its own peculiar conditions of life, under which alone it can flourish, and, as a consequence, its own special action on the system, so, too, each may have its own special destructive agency. The conditions necessary to the destruction of the germs of typhoid fever, of typhus fever, of diphtheria, of measles, may be as distinct and as varied as the conditions requisite to their vital

activity. An agency which destroyed one of them might have no action on the other.

Quinine may destroy the ague poison without having a like action on the poison of any other disease. The temporary effect which it has in lowering the body heat in other fevers is due to its action on the system. The speedy and lasting cure which it brings about in intermittent fever results not from this, but from its destructive action on the poison of that disease.

3. *The Treatment of Rheumatic Fever.*

In this, as in other fevers, a rational system of treatment presupposes a knowledge of the mode and production of the disease. A study of this subject led me some years ago to the conclusion that the rheumatic poison was not generated in the system, but was introduced into it from without; and that rheumatic fever was really malarial in origin. A study of the natural history of the disease seemed to indicate many analogies between it and ordinary malarial fever.[1]

1. Both are apt to occur in low-lying damp localities, in certain climates, and at certain seasons of the year.
2. Some people are more liable to be attacked than others.
3. They have no definite period of duration.
4. They are not communicable from the sick to the healthy.
5. In both the fever is irregular in type, and characterised by variations in its course.
6. In both there is a copious deposit of urates, and a tendency to profuse perspirations.
7. In each, one attack is said to render the system more liable to its recurrence.
8. Unless arrested by treatment, each may have a protracted and uncertain course.
9. Each is capable of being rapidly arrested by treatment.

[1] *On Rheumatism, its Nature, its Pathology, and its Successful Treatment.* By T. J. Maclagan, M.D. Pickering & Co: 1881.

The rheumatic poison, both in its history and in its effects on the system, seems to bear a closer analogy to the poison of an ordinary malarial fever than to any other morbific agency.

Adopting this view of the nature of the poison of rheumatic fever, believing it to be of miasmatic origin, and generically allied to, though specifically distinct from, the poison of ague; and keeping in view what we believed, and have now stated regarding the action of quinine on the ague poison, it seemed not unlikely that there might be found some agency capable of producing the same action on the rheumatic poison, and which, in virtue of that action, would cut short the course of acute rheumatism as quinine cuts short an ague. If one malarial fever could have its course arrested by quinine, it was probable that other malarial fevers might equally have their course arrested by other and probably allied agencies. Salicin, the active principle of the willow bark, seemed on reflection to be a likely agency to produce this result. Salicin was therefore prescribed. The result exceeded all expectations. Given in sufficient quantity, salicin was found to arrest the course of acute rheumatism as effectually as quinine arrests the course of intermittent fever.[1] In both cases insufficient doses lead to imperfect results; in both cases the too early omission of the remedy is followed by a return of the fever; but equally in both its continued use for some time after the fever is allayed, results in a permanent cure.

How does the salicin produce this result? Either it so acts on the system as to render it insusceptible to the action of the rheumatic poison, or it so acts on the rheumatic poison as to render it incapable of acting on the system. Which is it? All that was said regarding quinine in ague is, *mutatis mutandis*, applicable to salicin in rheumatism. It possesses, though in a less degree than quinine, the

[1] The two plants which occurred to me as most worthy of trial were the willow and the meadow sweet (*spiræa ulmaria*). It is to be noted that each contains an important salicyl compound: the willow bark contains salicin, the meadow sweet salicylous acid. The meadow-sweet oil is possessed of decided anti-rheumatic properties, but it is unpleasant to take, and has no special advantage.

power of temporarily lowering the temperature of the febrile body, but has no effect on that of the non-febrile. In virtue of their febrifuge properties, salicin and salicylic acid have been administered in various febrile ailments. Reiss has maintained that salicylic acid shortens the duration of typhoid fever. I have given both salicin and salicylic acid freely in both typhus and typhoid fevers, in pneumonia, in erysipelas, and other acute diseases, and have never found any evidence that they shortened the duration or diminished the mortality of any of these maladies.

It is with the salicyl compounds as it is with quinine; there is but one fever in which they exercise a distinctly curative action. In other fevers they may for a time lower the temperature, but in rheumatic fever alone do they arrest the course of the disease. But rheumatic fever does not consist solely of fever. An essential part of it is inflammation of the fibrous textures of the joints. Just as it is impossible for any poison to produce the disease without causing inflammation of these textures, so it is impossible for any remedy to cure it without allaying that inflammation. Fever and local inflammation are essential parts of the disease. Fever does not give rise to inflammation, but inflammation may give rise to fever; a remedy which acted solely as a febrifuge might allay the fever, but not the inflammation: but a remedy which put a stop to inflammation might thereby allay fever. As salicin and salicylic acid put a stop to the joint inflammation as well as to the fever, it is evident that it is not in virtue of their febrifuge action that they cure acute rheumatism. As it is only in rheumatic inflammation that they have this effect, and as they do not exercise the same curative action when the joints are inflamed from other than rheumatic causes, it is evident that their action is not directly on the inflamed textures. Salicin and salicylic do not cure by arresting fever, and do not cure by arresting joint inflammation, and yet they cure both. The only other way in which they can act is by arresting the rheumatic process—that which produces both the fever and the joint inflammation. In other words, the salicyl compounds act not on the sufferer, but on that which makes

him suffer; not on the system, but on the rheumatic poison. That poison we believe to be malarial in nature; malarial poisons we believe to be minute organisms; the only way in which the action of such organisms can be put a stop to is by destroying them; we believe, therefore, that the salicyl compounds cure rheumatic fever by destroying the poison which causes both the fever and the joint inflammation; hence the advisability of giving large and frequent doses, for the more speedily the system is saturated with the remedy, the more speedily and thoroughly will the poison be destroyed. The salicyl compounds are so quickly eliminated from the system that frequent repetition of a full dose is essential to their full beneficial action.

Intermittent fever and rheumatic fever stand out prominently as the two diseases over which medicine exercises the most marked control, and as the only two acute diseases whose course can be rapidly cut short. This very remarkable result is produced by remedies which, when taken in the same dose by healthy persons, produce little or no effect on the system. For reasons already given we regard their curative effects as the result not of their febrifuge properties, but of their destructive action on the poisons of these diseases. On no other view can the limitation of the curative action of quinine to malarial fever, and of salicin to rheumatic, be explained.

Should pneumonia be regarded as of miasmatic origin, like intermittent and rheumatic fevers, (a view in support of which much might be said), the discovery of a remedy capable of destroying the pneumonic poison, and arresting the course of that disease, may not unreasonably be anticipated. Some day we may even have the power thus to arrest the specific fevers. If phthisis, cancer, leprosy, and other constitutional maladies characterised by a local lesion owe their origin to special organisms, as is generally believed nowadays, it is possible that they too may some day have their course arrested by agencies which destroy their poisons without having any direct action on the system.

4. *The Action of Febrifuge Remedies.*

In the treatment of the maladies which have hitherto engaged our attention, febrifuges as such have found no place; for it is not in virtue of their febrifuge properties that quinine cures ague, or salicin cures rheumatism. Nevertheless febrifuge remedies do play an important part in the treatment of many febrile states. The part which they play, and the mode in which they play it, will be best seen by considering separately the action and uses of the different febrifuge remedies. The chief of these are cold, quinine, salicin and salicylic acid, antipyrin, antifebrin, and kairin.

Cold is the most powerful antipyretic we possess. In the most pronounced forms of neurotic fever—the hyperpyrexia of sunstroke and of rheumatic fever—it is the one remedy on which we rely. How does it act? The opinion generally held is that the cold allays the disturbance by lowering the temperature. But to say that the mere lowering of the body heat is sufficient to allay the alarming symptoms, is equivalent to saying that the symptoms are caused by the high temperature; and we have already seen that that is a position which cannot be maintained. The high temperature is not the cause of the alarming symptoms, it is simply one of them—one of the indications that the reins are slackened, that functional activity has got beyond the control of normal inhibition, and that the machinery of organic life is hurrying on at a dangerous pace. This view of the matter is well illustrated by what is observed in severe cases of cerebral hæmorrhage; the temperature rises soon after the hæmorrhage has taken place, and continues to rise up to the moment of death. Here the high temperature has nothing to do with the production of the alarming symptoms or the fatal result; the organic lesion is the cause of these and of the high temperature; and we look upon this rising temperature only as an important element in prognosis, and a sure sign that the case will prove

speedily fatal: we never think of it as the cause of the fatal termination. The rapid rise of temperature that takes place immediately before death in these cases is the indication that the reins have been cast loose, and that the machine is hurrying on to destruction.

Hyperpyrexia essentially consists in paralysis of inhibition of metabolism. Such paralysis may result either from organic lesion or functional disturbance of the nervous centres. The very high temperature to which the condition owes its name is in no case to be regarded as the cause of the alarming symptoms which accompany it, but only as one of the symptoms, and as the special indication that the function of heat inhibition is paralysed; just as the very rapid pulse (150 to 160) and the very frequent and hurried respiration indicate that the inhibition of the cardiac and respiratory functions is impaired. When hyperpyrexia is due to organic lesion treatment is of no avail. When due to functional disorder it may be cured. In the treatment of this condition the external application of cold is the remedy on which we chiefly depend. If the cold does not cure by allaying the heat, how does it act? If hyperpyrexia depends on paralysis of the function of heat inhibition, the remedy which allays it probably does so by stimulating that function into renewed activity.

Inhibition is essentially a quieting and calming agency, having its seat in the nervous centres, and exercising a controlling influence over the functions of life. Undue stimulation or activity of this inhibitory force might seriously impair these functions, and even bring life to an end. Complete inhibition of any of the essential functions of organic life means death. An instance of death brought about in this way we have in poisoning by digitalis; there death is due to excessive stimulation of the inhibitory nerve of the heart: by stimulating the vagus digitalis slows the heart's action till it ultimately stops in diastole. Another instance we have in death caused by cold. Cold has a markedly sedative action on the functions of organic life. One of the first indications of danger from undue exposure to it is drowsiness, a tendency to sleep. So powerful is

this tendency that it can with difficulty be resisted even by those who know that if once they give way to it the sleep will deepen into fatal coma.

Cold is thus a powerful agency, exercising a sedative action so great that it may even prove fatal by coma. But, like other sedatives, it may be used in moderation, and its quieting action turned to good account.

Hyperpyrexia is the condition in which it is most useful. As the action of cold in that condition is not temporary and palliative, but lasting and curative—as the cold not only reduces the high temperature but restores the normal balance, and brings again into play the normal inhibitory function—as it does all this, it is evident that cold produces its beneficial effects in neurotic fever by stimulating into renewed activity the inhibitory function of the nervous apparatus, impairment of which causes the rise of temperature. By a generally sedative action it might allay disturbance *while it was being applied*: but without restoring inhibition it could not cure, for cure in such a case means not only the lowering of the temperature but the complete restoration of the balance of metabolism.

The central thermal apparatus, that which presides over heat formation, heat inhibition, and heat elimination, is necessarily in free communication with the skin, for it is in the skin that sensations of heat and cold are felt, and it is through the skin that heat is eliminated. The nerves which receive the impressions of heat and cold must be connected with the centres in which these sensations are registered, and such centres must be associated with the function of heat inhibition. It is on the extremities of these nerves that the cold acts, and it is along these nerves that this peripheral excitation is transmitted to the inhibiting centres: the action is essentially a stimulant one: but to stimulate inhibition is the physiological and scientific method of allaying undue functional activity. Just as heat (as in heat apoplexy) paralyses inhibition and thus causes the temperature rapidly to rise, so cold stimulates inhibition and thus causes this abnormal temperature to fall. Just as it is not the direct heating up of the body

by the hot atmosphere that causes the very high temperature of heat apoplexy, so it is not the direct cooling action of cold on the body that cures this condition. The heat acts by impairing, maybe even paralysing, the function of inhibition: the cold acts by stimulating that function into renewed activity. Its action in this respect may be compared with, and illustrated by, the action of digitalis in some forms of heart disease. When we find the heart acting in an unnecessarily disturbed and excited manner, as it frequently does in mitral disease, we do not combat this condition by efforts tending directly to soothe the excito-motor nerve of the heart: no, we rather gain our object indirectly by giving digitalis and stimulating to increased activity the counterbalancing force—the cardiac inhibitory nerve—the vagus. In doing so we adopt a line of treatment which is not only found in practice to be the most successful, but is also the most scientific, and the most in accord with the teachings of physiology and the operations of nature.

Such is the mode of action of cold: it allays disturbance by stimulating the inhibitory, or calming and restraining, functions of life. In using it care must be taken not to give an overdose, for excessive stimulation of inhibition would arrest functional activity and cause death.

Equally, care must be taken not to employ it in unsuitable cases. Unsuitable cases are those in which inhibition of metabolism is not impaired. This brings us to the consideration of the question of its clinical value in the treatment of fever.

In discussing this question care must be taken to distinguish between metabolic and neurotic fever—between rise of temperature consequent on increased production of heat, and rise of temperature consequent on defective inhibition of heat. Metabolic fever results from the propagation of minute organisms in the system. The disturbance which constitutes the fever is produced by an agency introduced into the system from without (the fever poison)—an agency which has no connection whatever with the system, and over which the nervous centres can exercise no control.

So long as this poison continues to be reproduced in the tissues and to cause increased consumption of nitrogen and water, so long will it cause increased metabolism and consequent fever; and nothing but destruction of the poison, or exhaustion of the second factor necessary to its reproduction, can arrest the course of the disease. Such fever cold cannot cure. In any fever the application of cold, if continued long enough, will of course lower the temperature; but the cold necessary to do this might so depress the patient as to interfere with his recovery. Not to lower the temperature, but to mitigate the severity of the disease, is the object in view.

Cold acts by causing increased activity of that inhibitory function by which tissue metabolism is kept within due bounds. But what are due bounds and what undue?

A due amount of tissue metabolism is that which necessarily results from the changes taking place in the tissues. An undue amount is anything in excess of this. While inhibition is unimpaired the due amount is not exceeded. It may, as in the specific fevers, be in excess of the metabolism of health; but it is not in excess of that which necessarily results from the propagation of the poison in the tissues; it is not, therefore, in undue amount.

An undue amount of tissue metabolism can result only from defective inhibition. It follows from this that the terms 'due' and 'undue,' as applied to the amount of metabolism in fever, correspond to the terms 'metabolic' and 'neurotic.' In metabolic fever the rise of temperature is no more than necessarily results from the changes which must go on while the morbid process continues. In neurotic fever the rise of temperature is in excess of what would result from the necessary metabolism, because metabolism itself is in excess of what is necessary. Such excess can result only from defective inhibition.

In morbid conditions in which the rise of temperature is no more than must result from the necessary metabolism, cold as an antipyretic can have no curative action, and may even do harm. In morbid conditions in which the rise of temperature is in excess of that due to the necessary

tissue metabolism, cold may do much good; for such excess results from defective inhibition of heat, and the action of cold is to stimulate this function into renewed activity. How are we to recognise such cases? How discriminate between the suitable and the unsuitable?

In neurotic fever there is not much difficulty, for in all cases due bounds are passed, in all cases there is defective heat inhibition, and in all cases the external application of cold is a suitable remedy. Theoretically this treatment is applicable to all cases in which the rise of temperature is of neurotic origin. Practically, and for purposes of clinical demonstration, such cases may be divided into three classes:—

1. Those, such as ephemeral fever, in which the rise of temperature is so slight or so transient that no special treatment is necessary.

2. Those, such as cerebral hæmorrhage, in which the rise of temperature is the result of an organic lesion, and in which the lowering of the body heat by cold could do no possible good.

3. Those, such as heat apoplexy and rheumatic hyperpyrexia, in which the rise of temperature is due to functional disorder of heat inhibition. It is in these cases that the beneficial effects of cold are most marked. The vigorous use of this remedy is indeed the most, I had almost said the only, effective and successful mode of treating them.

In fever of metabolic origin there would be no difficulty if it remained purely metabolic, for due bounds would not be passed, and cold as an antipyretic would have no place in its treatment. But generally there is superadded to the increased heat resulting from increased tissue metabolism a certain amount due to defective inhibition. How is this induced? In one of two ways:—

(1) Heat inhibition exists for the purpose of restraining undue heat formation; in metabolic fever heat formation is in excess; a necessary result of excessive heat formation is stimulation of heat inhibition. Continued stimulation of any function may result in fatigue (witness the loss of func-

tion which results from tetanising a muscle), fatigue leads to defective performance of function; this, in the case of heat inhibition, would lead to rise of temperature; and thus in any case of metabolic fever we may have superadded a certain amount of neurotic fever, which may even culminate in hyperpyrexia, as was pointed out when considering the pathogenesis of that condition (page 33).

(2) Then, again, metabolic fever is idiopathic; occurs, that is to say, independently of any local inflammatory lesion. But such lesions are common in the course of idiopathic fevers, and even form an essential feature in their history, as in the bowel lesion of typhoid fever, the throat lesion of scarlatina, and the chest complications of measles. It cannot for a moment be denied that such lesions cause some increase of the general febrile disturbance; we thus have superadded to the idiopathic a certain amount of symptomatic fever, and a corresponding increase in the general disturbance.

Symptomatic fever is generally, possibly always, of neurotic origin. With one or both of these two modes of inducing neurotic fever at work in all cases of metabolic fever, it is probable that purely metabolic fever is the exception, and that in the majority of cases the existence of some degree of neurotic fever has to be allowed for in treatment. It is not possible in any case to indicate the exact point at which the rise of temperature due to increased metabolism ends, and that resulting from defective inhibition commences. It is not possible, therefore, to indicate the exact point at which the sphere of usefulness of cold commences. Nevertheless, there is seldom any practical difficulty in deciding the point in a given case, and in using the remedy aright, if we are careful only to keep before us the difference between metabolic and neurotic fever, and to bear in mind that in metabolic fever it cannot cure, and may do harm; and that in neurotic fever it can do no harm, and may do much good, if properly used. If properly used: that is most important. In the treatment of fever the dose of cold varies as much as the dose of opium in the treatment of pain. In the severe agony of a nephritic or hepatic

colic we may with nothing but advantage give a dose of opium, which would be inadmissible in slighter pain. In hyperpyrexia we may with nothing but advantage apply cold with a vigour and decision which would be uncalled for, and might be disastrous, in an ordinary case of fever.

Rheumatic hyperpyrexia is the form of hyperpyrexia which we most frequently see. Before these days of accurate thermometry the amount of febrile disturbance was judged of by the rapidity of the pulse and the gravity of the general symptoms. What we now call 'rheumatic hyperpyrexia' our fathers called 'cerebral rheumatism.' I am not sure that the old name is not the better of the two. It indicates that the condition is of rheumatic origin, and that cerebral disturbance is the cause of the alarming symptoms. In so doing it expresses all that a name can express, and conveys to the mind a clear and definite idea of the nature and pathogenesis of the morbid condition which has to be dealt with. The term 'hyperpyrexia,' on the other hand, conveys no such definite idea: it simply draws prominent attention to one of the leading symptoms: any idea which it conveys of the pathogenesis of the condition is the misleading one that the high temperature is the cause of the disturbance, ignoring the patent fact that the high temperature itself has to be accounted for. But though pathologically misleading, the term 'hyperpyrexia' has its advantages, for it expresses a clinical fact of much practical importance, which has led to a successful plan of treatment. It had been abundantly demonstrated in the case of heat apoplexy, in which there is also hyperpyrexia, that the application of ice or cold water to the surface of the body gave the best chance of recovery. The malady being caused by great heat, the propriety of the application of cold as a remedy was obvious. The remedy which was found to be of service in the hyperpyrexia of heat apoplexy was naturally applied in the hyperpyrexia of acute rheumatism, and with the best results: and no other means of treatment is now advocated. In hyperpyrexia the danger is so great, and the symptoms so urgent, that

treatment must be prompt and vigorous; inhibition, one of the most important functions of organic life—one which is absolutely essential to the continuance of life—is all but paralysed. The remedy is the application in full dose of that which stimulates it into increased activity: that remedy is the external application of cold. Ice to the surface, pouring cold water over the body, wrapping it in a cold pack, putting it in a cold bath, are the active means by which inhibition is stimulated and the hyperpyretic condition subdued in urgent cases. In cases in which the danger is less urgent a tepid bath or tepid sponging may suffice; but in all the principle is the same, the application to the surface of the body of water having a much lower temperature than the body. Where the temperature is very high and the danger very urgent, rubbing the body with ice or putting in a cold bath till the temperature falls to below 100° is the most speedy means of attaining the desired end, care being taken not to cause too great depression. Where the danger is less urgent the desired end is sufficiently attained by keeping ice applied to the head, and by, at the same time, frequently sponging the body with cold or tepid water. The plan which I have found most simple and efficacious in such cases is to keep flipping the surface of the body, now the chest and abdomen, now the back, and now the limbs, with a sponge slightly moistened with cold or tepid water; the sponge should be soft, of loose texture, not more than two inches thick, and four to six inches in diameter. A sponge of that sort is easily flopped lightly and rapidly up and down on the surface; the fanning action by which this is done aids the action of the water in producing the stimulant action on the peripheral extremities of the nerves by which the desired impression is conveyed to the heat-inhibiting centre; it tends also to promote heat elimination. The practice of treating fever by cold baths is an old one which had fallen into disuse. The good results got from this treatment in hyperpyrexia led to its revival. If the high fever which has to be dealt with in hyperpyrexia could be thus cured, might we not also by the same agency arrest the more

moderate disturbance of an ordinary pyrexia? Such was the train of thought. Natural enough, but founded on a fallacy. It assumes that the two morbid conditions are similar in nature, and that hyperpyrexia is an exaggeration of pyrexia. But we have seen that they are essentially different in their mode of production, that hyperpyrexia is of neurotic origin, dependent on impaired inhibition, while pyrexia (that of idiopathic fever at least, which is the form of fever chiefly dealt with) is of metabolic origin, dependent on increased production of heat. Its curing hyperpyrexia is no proof that cold can cure pyrexia. And experience shows that it does not; for though some German physicians have tried to show that the course of typhoid fever may be arrested by the cold bath, these results are not accepted in this country, and the statistics by which they have attempted to prove them are not regarded as of much value.

Does cold, then, have no place in the treatment of fever of metabolic origin? It has a most important place, and is of much service in such fever. In purely metabolic fever it could do no good; but fever rarely is purely metabolic. It has already been stated that the continuance of metabolic fever for any length of time, or to a marked extent even for a short time, is likely, through over-stimulation, to lead to impairment of heat inhibition, and to the consequent superaddition to the metabolic of a certain amount of neurotic fever; and that a local lesion equally leads to the same result. As all metabolic fevers do continue for some time, and as most have a local lesion, it follows that there is along with the metabolic generally, if not always, some degree of neurotic fever. It is in the treatment of this that cold is so useful. As hyperpyrexia essentially consists in paralysis of inhibition of metabolism, the neurotic fever which has here to be dealt with essentially consists in impairment of that function. Such impairment not only gives a higher temperature than we should otherwise have, but makes the patient restless and uncomfortable, prevents proper sleep, and interferes in every way with the functions of life. The external application of cold stimulates inhi-

bition; stimulation of inhibition is the natural and physiological method of calming undue excitation; and thus in fever cold allays many of the symptoms which impart irksomeness and maybe even danger. In pyrexia the symptoms of impaired inhibition are less marked, and the danger less urgent than in hyperpyrexia; the same dose of cold, therefore, is not required. Instead of applying ice to the surface, or putting the patient in a cold bath, it is sufficient to wrap him in a wet sheet, or to sponge the body frequently with cold or tepid water. A rapid flopping of the surface of the body with a sponge moistened with water of a temperature of from 80° to 90° F. is generally sufficient. There are few cases of fever in which such treatment is not at once grateful and beneficial to the patient. Here the mode of action of the cold is the same as in hyperpyrexia. It soothes less by abstracting heat than by stimulating inhibition—nature's calming agency; though there can be little doubt that it also increases heat elimination. In all cases of fever in which the temperature tends to rise, or in which the patient is restless or sleepless, cold or tepid sponging is of service. By the regular use of cold in this way in all cases of pyrexia, the chance of the occurrence of hyperpyrexia is diminished, for by it the function of heat inhibition is regularly stimulated, and the risk of impairment of this function passing into paralysis proportionally decreased. The mode of application of the cold must vary with the urgency of the febrile symptoms. The important thing is that we should recognise that the cold allays the disturbance, not by abstracting the superfluous heat, but by stimulating inhibition, and preventing excessive tissue metabolism, and the troublesome, maybe even disastrous, consequences resulting therefrom. Important it is, too, to bear in mind that such stimulation may be excessive, and that such excess might cause death. It is never necessary to lower the temperature below 100° F. It is not necessary to do so, but it is not always possible to stop at that point, for frequently the temperature goes on falling after the cold is removed. When the temperature falls to that point the cold should be stopped, for cold, like digitalis, is cumulative

in its action; if given in sufficient dose its stimulant action on the inhibitory function continues for some time after the remedy has ceased to be applied—in the same way as we find the stimulant action of digitalis on the vagus continue for some time after the use of the drug is stopped; by means of digitalis we may reduce the frequency of the heart's action from 120 to 80; we may then omit the digitalis, but find the frequency of the cardiac action fall 20 or even 30 beats lower for two or three days after it is omitted. By means of the cold bath or of ice to the surface we may lower the temperature from 110° to 100° in a short time; we may then omit the treatment, but still find the temperature go on falling for some hours, and even going one or two degrees below the normal. Remedies which are cumulative in their action require to have their effects carefully watched. Cold is distinctly cumulative. For that reason its action has to be watched. As soon as the temperature is below 100° the treatment should be omitted; to be resumed if necessary.

Judiciously used in the manner indicated, cold is of much service in fever. In urgent cases of hyperpyrexia it should be given at once in full dose, that is, ice or ice-cold water should be applied to the whole surface. In cases in which fever runs high, but in which the stage of pyrexia is not exceeded—that is to say, when the temperature ranges from 104° to 106°—cold sponging of the body with ice to the head will generally suffice. In cases in which it ranges from 102° to 104°, sponging with water from 80° to 90° F. will generally suffice. In cases in which it does not exceed 102°, cold, as an antipyretic, is not called for, but tepid sponging is grateful to the patient, and it is not improbable that its regular use may, by gently stimulating inhibition, prevent that function from failing, and neurotic pyrexia from being developed.

Quinine.—Next to cold, quinine is the febrifuge which enjoys the highest reputation. Much of this reputation it owes to its curative effects in malarial fevers. But when considering its mode of action in these diseases, we saw that it was not in virtue of its febrifuge properties, but in virtue of

its action as a germicide, that it cured them—that its action was exercised, not on the disturbed system, but on the poison which produced the disturbance. It is not, therefore, in connection with malarial fevers that the febrifuge action of quinine has to be studied. But, to rob quinine of the reputation as an antipyretic which has accrued to it from its curative effects in ague is to cut away the chief foundation on which that reputation rests, and to distinctly lower its place in the list of antipyretics. It still, however, retains its place among them.

It has been shown by numerous observers that, though quinine does not lower the body heat in health, it nevertheless possesses the power of lowering it in many febrile ailments. All observers agree that, except in malarial fever, this effect is temporary—lasting only for a few hours. Besides lowering the temperature, quinine also very materially lessens the excretion of urea and uric acid, as was demonstrated first by Ranke, and subsequently by Kerner. The latter observer found that when nine grains a day were taken in divided doses, the elimination of urea was lessened $\frac{1}{8}$, and that of uric acid nearly $\frac{1}{2}$. Where a large dose (38 grains) was taken in the morning the urea was decreased $\frac{1}{4}$, and the uric acid about $\frac{4}{5}$. The result of the administration of quinine in adequate dose is thus to cause decreased formation of heat and decreased elimination of urea and uric acid. As these are the products of tissue metabolism, and as nothing but tissue metabolism can lead to their formation, it is evident that quinine produces its antipyretic effects by lessening tissue metabolism. How does it do this? We know of only one way in which functional activity can be restrained, and that is by stimulating inhibition. There is no other way in which the effects which we find quinine produce can be brought about; and there is no escaping the conclusion that quinine owes its antipyretic action to its power of inhibiting tissue metabolism. Its mode of action, therefore, is similar to that of cold, only the inhibiting centres are stimulated directly in the case of quinine—indirectly (by peripheral excitation) in the case of cold. But the action of quinine is only temporary. It

gives a fillip to inhibition, but it does not possess the cumulative or lasting action of cold. As compared with cold its action is feeble; even with all the stimulation that quinine can give, the inhibiting centres soon again become fatigued, the fever-producing cause asserts its superior force, metabolism is again in excess of inhibition, and the fever runs its course uninfluenced by what has taken place.

Though malarial fevers are those in which the curative and germicide action of quinine is most pronounced, I am not sure that they are the only ones in which it is found. The remarkable and lasting curative action which I have on several occasions seen large doses of quinine produce in some forms of blood poisoning has led me to think that its action in these cases was that of a germicide rather than that of an antipyretic.

The Salicyl Compounds.—It cannot be said that there is any other febrile ailment than acute rheumatism in which these compounds exercise a distinctly curative action. In that disease they do cure very rapidly; and it is mainly on their power of arresting the course of the febrile symptoms in rheumatic fever that their antipyretic reputation rests. But when considering the treatment of that disease we gave our reasons for the belief that their curative effect depended, not on any action which they had on the system, but on their action on the rheumatic poison—that they arrested the course of acute rheumatism, not in virtue of any antipyretic action, but in virtue of their destructive action on the rheumatic poison. To rob these compounds of the antipyretic reputation derived from their curative effect in rheumatic fever is to place them very low in the list of antipyretics. Nevertheless that is their proper place. They have their actions and uses; but, as antipyretics, salicin and salicylic acid are inferior to quinine, and much inferior to antipyrin and antifebrin. It is to their anti-rheumatic action that they owe the high place which they occupy in the physician's armamentarium. What antipyretic action they

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do possess is probably exercised in the same way as that of quinine—by a temporary excitation of the inhibiting centres.[1]

Antipyrin, *Antifebrin*, and *Kairin*, though they do not, so far as we know, possess the power of curing any specific fever, as quinine cures ague or the salicyl compounds cure rheumatism, are nevertheless more active antipyretics than quinine or salicylic acid. As antipyretics they rank next to cold. They are not at all to be regarded as substitutes for cold in the treatment of hyperpyrexia; but in cases of fever in which the temperature rises unduly, whether this rise is or is not accompanied by restlessness and a disturbed condition of the nervous system, an occasional dose of antipyrin, or antifebrin, often suffices to allay the fever and subdue any nervous symptoms which accompany

[1] Dr. Latham (*Croonian Lectures*, 1886) has adduced a very elaborate chemical argument in support of the hypothesis that rheumatism is of neurotic origin, and due to ehanges in the medulla oblongata. A careful perusal of Dr. Latham's lectures shows that he has not sufficiently differentiated between rheumatism and other allied disorders. Rheumatism is essentially a disease *per se*, as distinet from all others as is a pneumonia or an ague. Acute rheumatism, rheumatoid arthritis, and the osseous changes which take place in Charcot's disease, represent three morbid eonditions as different in their nature and in their pathogenesis as are pneumonia, asthma, and pulmonary emphysema; but in Dr. Latham's leetures they are mixed up in a manner which implies pathologieal allianee, and makes it at times diffieult to know which morbid eondition he is referring to.

Much of what Dr. Latham says regarding the action of benzoic and salieylic acids is interesting in its relation to gout, but has very little bearing on the treatment of rheumatism. He says, moreover, that 'the true salicylic acid obtained from the vegetable kingdom must alone be employed.' Dr. Latham gives no evidence to support a statement whieh is opposed to almost universal experience. He asserts that the natural salicylie acid produces none of the disturbing effects whieh follow the use of the artificial. My experienee is different. I have seen it produce these effects on several oeeasions. I have used salicin, natural salicylie acid, artificial salicylic acid, saliritin, saligen, and salol—all freely. They are all valuable anti-rheumatics, but the only one which in my experience has never produced any disturbance of the heart or brain is salicin. Salieín possesses all the advantages elaimed by Dr. Latham for natural salieylie acid; it is obtained from the vegetable kingdom, and is a natural produet. It is, moreover, very mueh cheaper than natural salicylie acid; its general aetion on the system is tonie rather than depressing.

it. The lowering of the temperature is accompanied by diminished frequency of the heart's action and lessened excretion of nitrogenous compounds.

These remedies are of great practical utility in the treatment of fever. When the temperature tends to rise up unduly, twenty grains of antipyrin or antifebrin given once or twice a day often suffices to keep it at a lower level. In cases of acute rheumatism in which hyperpyrexia threatens, there may often, if not always, be noted certain premonitory signs which should lead one to be on the outlook; the patient is restless, has an anxious expression, a sense of discomfort and apprehension which he cannot explain. 'I don't know what is the matter, but I feel very queer,' was the remark made by a lady suffering from an ordinary attack of acute rheumatism, whose temperature at the time was 102°, but in whom hyperpyrexia was developed that night. Commencing failure of inhibition of metabolism is the cause of the condition. In such cases the skin, instead of perspiring freely, as it normally does in acute rheumatism, is hot and dry. Heat inhibition and heat elimination are functionally allied: it is probable that when heat inhibition is paralysed heat elimination is also interfered with; and that the dry unperspiring skin is a result rather than a cause of the hyperpyretic state. Cold to the surface is the best remedy for this condition, but where that treatment is not convenient, or where for any reason it may be considered not quite suitable, very good results may be got from the frequent administration of antipyrin in ten to twenty grain doses. Twenty grains of salicin and ten to twenty of antipyrin given every hour for three or four hours I have found give excellent results in such cases; and have little doubt that by this treatment hyperpyrexia may sometimes be warded off—the salicin curing the rheumatism and the antipyrin stimulating the inhibiting centre, and so preventing the consequences of impairment of that function. After the alarming symptoms of a fully developed hyperpyrexia have been allayed by cold, antipyrin or antifebrin may be given with much

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